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(71) Applicant *(for all designated States except US)*: **AGOURON PHARMACEUTICALS, INC.** [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SUN, Eric, T.** [US/US]; 4281 Kerwood Court, San Diego, CA 92130 (US). **ANDERSON, Mark, B.** [US/US]; 41 Las Cascadas, Orinda, CA 94563 (US). **ANDERES, Kenna, L.** [US/US]; 11122 Corte Mar De Cristal, San Diego, CA 92130 (US). **CHRISTIE, Lance, C.** [US/US]; 518 Mynah Place, Vista, CA 92083 (US). **DO, Quyen-Quyen, T.** [US/US]; 11886 Cypress Valley Drive, San Diego, CA 92131 (US). **FENG, Jun** [CN/US]; 3536 Corte Yolanda, Carlsbad, CA 92009 (US). **GOETZEN, Thomas** [US/US]; 6227 Lorca Drive, San Diego, CA 92115 (US). **HONG, Yufeng** [US/US]; 11980 Ashley Place, San Diego, CA 92128 (US). **IATSIMIRSKAIA, Eugenia, A.** [RU/US]; 10680 Arbor Heights Lane, San Diego, CA 92121 (US). **LI, Haitao** [CN/US]; 11331 W. San Raphael Driveway, San Diego, CA 92130 (US). **LUTHIN, David, R.** [US/US]; 1772 Shadow Mountain Drive, Encinitas, CA 92024 (US). **PADERES, Genevieve, D.** [US/US]; 5183 Sea Mist Ct., San Diego, CA 92121 (US). **PATHAK, Ved, P.** [US/US]; 4140-157 Via Candidiz, San Diego, CA 92130 (US). **RAJAPAKSE, Ranjan, Jagath** [US/US]; 13628, Pomerado Road, #14, Poway, CA 92064 (US). **SHACKELFORD, Scott** [US/US]; 672 West Via Rancho Parkway, Escondido, CA 92029 (US). **TOMPKINS, Eileen, Valenzuela** [US/US]; 10129 West Lilac Road, Escondido, CA 92026 (US). **TRUESDALE, Larry, K.** [US/US]; 10382 Rue Chamberry, San Diego, CA 92131 (US). **VAZIR, Haresh** [US/US]; 305 Kern Street, Salinas, CA 93905 (US).

(74) Agent: **HADDACH, Aubrey, A.**; Agouron Pharmaceuticals, Inc., Legal Division, Patent Dept., 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).

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(54) Title: NON-PEPTIDE GNRH AGENTS, PHARMACEUTICAL COMPOSITIONS AND METHODS FOR THEIR USE, AND PROCESSES FOR PREPARING THEM AND THEIR INTERMEDIATES

(57) Abstract: Non-peptide GnRH agents capable of inhibiting the effect of gonadotropin-releasing hormone are described. Such compounds and their pharmaceutically acceptable salts, prodrugs, and active metabolites are suitable for treating mammalian reproductive disorders and steroid hormone-dependent tumors as well as for regulating fertility, where suppression of gonadotropin release is indicated. Methods for synthesizing the compounds and intermediates useful in their preparation are also described.

NON-PEPTIDE GnRH AGENTS, PHARMACEUTICAL COMPOSITIONS AND METHODS FOR THEIR USE, AND PROCESSES FOR PREPARING THEM AND THEIR INTERMEDIATES

TECHNICAL FIELD AND INDUSTRIAL APPLICABILITY OF THE INVENTION

This invention relates generally to compounds that affect the action of human gonadotropin-releasing hormone (GnRH). More particularly, it relates to non-peptide GnRH antagonists or agonists and to their preparation. These non-peptide GnRH agents have advantageous physical, chemical, and biological properties, and are useful medicaments for diseases or conditions mediated by modulation of the pituitary-gonadal axis. The invention also relates to methods for treating individuals needing therapeutic regulation of GnRH--i.e., methods for treating diseases and conditions mediated by GnRH regulation. The invention further relates to processes for synthesizing intermediate compounds useful for making GnRH agents.

BACKGROUND OF THE INVENTION

Gonadotropin-Releasing Hormone (GnRH), also known as luteinizing hormone-releasing hormone (LH-RH), plays a central role in the biology of reproduction. A large variety of analogs have been used for an increasing number of clinical indications. The GnRH decapeptide (pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 or p-EHWSYGLRPG-NH_2) is produced in neurons of the medial basal hypothalamus from a larger precursor by enzymatic processing. The decapeptide is released in a pulsatile manner into the pituitary portal circulation system where GnRH interacts with high-affinity receptors (7-Transmembrane G-Protein Coupled Receptors) in the anterior pituitary gland located at the base of the brain. In the pituitary, GnRH triggers the release of two gonadotropic hormones (gonadotropins): luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In testes and ovaries, LH stimulates the production of testosterone and estradiol, respectively. FSH stimulates follicle growth in women and sperm formation in men. When correctly functioning, the pulse-timed release and concentration levels of GnRH are critical for the maintenance of gonadal steroidogenesis and for normal functions of reproduction related to growth and sexual development.

The pituitary response to GnRH varies greatly throughout life. GnRH and the gonadotropins first appear in the fetus at about ten weeks of gestation. The sensitivity to GnRH declines, after a brief rise during the first three months after birth, until the onset of puberty. Before puberty, the FSH response to GnRH is greater than that of LH. Once puberty begins, sensitivity to GnRH increases, and pulsatile LH secretion ensues. Later in puberty and throughout the reproductive years, pulsatile release of GnRH occurs throughout the day, with LH responsiveness being greater than that of FSH. Pulsatile GnRH release results in pulsatile LH and FSH release from the pituitary, and hence, estosterone and estradiol release from the gonads. After menopause, FSH and LH concentrations rise, and post-menopausal FSH levels are higher than those of LH.

Chronic administration of GnRH agonists and antagonists to animals or to man results in decreased circulating levels of both LH and FSH. GnRH agonists are compounds that mimic endogenous GnRH to stimulate receptors on the pituitary gland, resulting in release of LH and FSH. After a transient rise in gonadal hormone production or "flare" response, chronic administration of GnRH agonists results in a down-regulation of GnRH receptors. GnRH receptor down-regulation and desensitization of the pituitary results in a decrease of circulating levels of LH and FSH. In spite of the symptom-exacerbating hormonal flare experienced, GnRH agonists have been the treatment of choice for sex-steroid-dependent pathophysiologies. For example, GnRH agonists have been used to reduce testosterone production, thereby reducing prostate volume in benign prostatic hyperplasia (BPH) and slowing tumor growth in prostate cancer. These compounds have also been used to treat breast and ovarian cancers.

Recently, GnRH antagonists have become available for clinical evaluation. GnRH antagonists have an immediate effect on the pituitary without the observed flare associated with agonists. Use of GnRH antagonists (usually decapeptides) has been reported in the literature for treatment of breast, ovarian, and prostatic cancers. Other uses of antagonists, like agonists, include endometriosis (including endometriosis with pain), uterine myoma, ovarian and mammary cystic diseases (including polycystic ovarian disease), prostatic hypertrophy, amenorrhea (e.g., secondary amenorrhea), and precocious puberty. These compounds may also be useful in the symptomatic relief of premenstrual syndrome (PMS). Furthermore, antagonists may be useful to regulate the secretion of gonadotropins in male mammals

to arrest spermatogenesis (e.g., as male contraceptives), and for treatment of male sex offenders. Importantly, GnRH antagonists (and agonists) have found utility in treatments where a reversible suppression of the pituitary-gonadal axis is desired.

For over fifty years, androgen deprivation has been the most effective systematic therapy for the treatment of metastatic carcinoma of the prostate. The rationale is simple—the prostate gland requires androgens for proper growth, maintenance, and function. Yet, prostate cancer and benign prostate hyperplasia are common in men and develop in an environment of continuous androgen exposure. Thus, utilizing a GnRH antagonist to interrupt the pituitary-gonadal axis reduces androgen production and results in tumor growth modulation. Furthermore, GnRH antagonists may have a direct effect on tumor growth by blocking receptors on the tumor cells. For those cancer types that respond both to sex hormones and to GnRH directly, antagonists should be effective in slowing tumor growth by these two mechanisms. Since GnRH receptors are present on many prostate and breast cancer cells, it has recently been speculated that GnRH antagonists may also be effective in treating non-hormone-dependent tumors. Recent literature examples indicate that GnRH receptors are present on a number of cancer cell lines, including:

- prostate cancer: GnRH agonists exert both *in vitro*, and *in vivo*, a direct inhibitory action on the growth of both androgen-dependent (LNCaP) and androgen-independent (DU 145) human prostatic cancer cell lines [Montagnani et al., *Arch. Ital. Urol. Androl.*, 69(4), 257-263 (1997); "GnRH Antagonist Inhibit the Growth of Androgen-Independent PC-3 Prostate Cancer in Nude Mice," Jungwirth et al., *Prostate*, 32(3), 164-172 (1997)];
- ovarian cancer: The demonstration of GnRH receptors in human ovarian cancers provides a rationale for the use of therapeutic approaches based on GnRH analogues in this malignancy [Srkalovic et al., *Int. J. Oncol.*, 12(3), 489-498 (1998)].
- breast cancer: Breast cancer is the most common type of cancer in women over the age of forty and is the leading cause of cancer-related death in women. Systematic endocrine intervention represents a major treatment option for the management of advanced breast cancer, especially with estrogen-dependent cancers. The genes for gonadotropin-releasing hormone

and its receptor are expressed in human breast with fibrocystic disease and cancer [Kottler et al., *Int. J. Cancer*, 71(4), 595-599 (1997)].

GnRH agents may also be useful in treating cancer through generation of thymus re-growth and therefore induction of the development of new T-cells. See Norwood Abbey press release dated March 5, 2001. These white blood cells, which develop in the thymus gland, are a fundamental component of the immune system's involvement in a range of diseases, including viral infections, transplant organ rejection, cancer, and autoimmune diseases. Thus, for example, since the human immunodeficiency virus (HIV) preferentially infects and destroys T-cells, GnRH agents may be useful for treating HIV infection or acquired immune deficiency syndrome (AIDS). Additionally, GnRH agents may be useful in combating infection in tissue-transplant patients where immunosuppressive drugs, which remove T-cells, are being administered to counteract rejection of the transplanted tissue. Similarly, since adequate and effective T-cells help defend against cancer, and chemotherapy and radiation regimens detrimentally impact T-cells, GnRH agents may be useful in treating cancer. Furthermore, GnRH agents may be useful for treating autoimmune diseases such as multiple sclerosis (MS), where T-cells are produced that react against a molecule surrounding nerve cells.

Heretofore, available GnRH antagonists have primarily been peptide analogs of GnRH. See, e.g., International Publication Nos. WO 93/03058, WO 99/50276, WO 00/12521, and WO 00/12522; Koppan et al., *Prostate*, 38(2),151-8 (1999); and Nagy et al., *Proc Natl Acad Sci USA*, 97(2),829-34 (2000). Though peptide antagonists of peptide hormones are often quite potent, the use of peptide antagonists is typically associated with problems because peptides are degraded by physiological enzymes and often poorly distributed within the organism being treated.

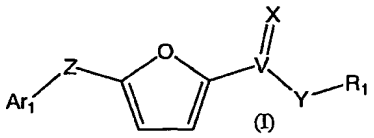
The first non-peptide antagonist of the human leuteinizing hormone-releasing hormone (LHRH) receptor was reported by Cho et al. (*J Med Chem*, 41(22), 4190 (1998). Since then, other non-peptide GnRH antagonists have been reported in the literature. For example, quinolone-6-carboxamides were reported by Walsh et al. in *Bioorg & Med Chem Ltrs.*, 10, 443-447 (2000). Tricyclic diazepines and cyclic pentapeptides were reported in International Publication Nos. WO 96/38438 and WO 96/34012, respectively. Tetrahydroisoquinoline derivatives were reported in U.S. Patent No. 5,981,521. For additional examples of non-peptide GnRH antagonists, see International Publication Nos. WO 97/21435, WO 97/21703, WO 97/21704, WO

97/21707, WO 99/44987, WO 00/04013, WO 00/12522, WO 00/12521, WO 00/04013, and WO 00/20358.

Despite recent advances, there continues to be a need for non-peptide antagonists of the peptide hormone GnRH with desirable properties. For example, there is a need for non-peptide GnRH agents having advantageous physical, chemical and biological properties compared to peptides, which are useful medicaments for treating diseases mediated via the pituitary-gonadal axis and by directly targeting the receptor on tumor cells. There is also a need for GnRH agents that act upon these receptors to treat both hormone-dependent and hormone-independent cancers.

SUMMARY OF THE INVENTION

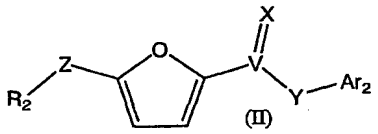
In one general aspect, the invention is directed to compounds represented by the following Formula I:



(I)

wherein the variables are as defined in the claims.

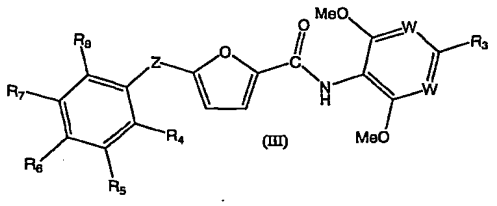
In another general aspect, the invention is directed to compounds represented by Formula (II):



(II)

wherein the variables are as defined in the claims.

In a further general aspect, the invention is directed to compounds represented by Formula (III):



(III)

wherein the variables are as defined in the claims.

In addition to compounds of Formulas I, II, and III, the invention is also directed to pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically

acceptable salts of such metabolites. Such compounds, salts, prodrugs and metabolites are at times collectively referred to herein as "GnRH agents."

The invention also relates to pharmaceutical compositions each comprising a therapeutically effective amount of a GnRH agent of the invention in combination with a pharmaceutically acceptable carrier or diluent. Moreover, the invention relates to methods for regulating the secretion of gonadotropins in mammals, comprising administering therapeutically effective amounts of GnRH agents of the invention.

Other aspects, features, and advantages of the invention will become apparent from the detailed description of the invention and its preferred embodiments.

DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

As used herein, the terms "comprising" and "including" are used herein in their open, non-limiting sense.

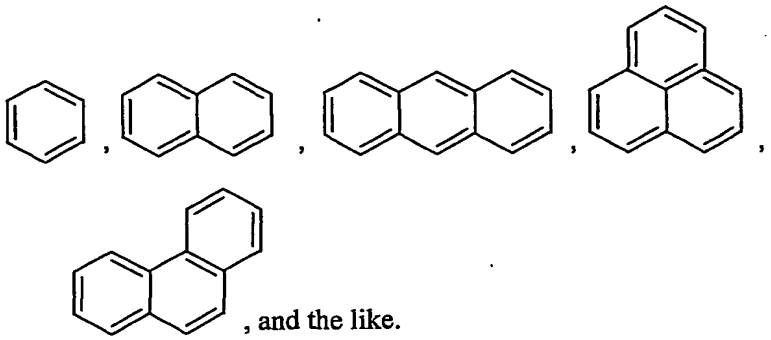
The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Exemplary alkyl groups include methyl (Me, which also may be structurally depicted by /), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

The term "heteroalkyl" refers to a straight- or branched-chain alkyl group having from 2 to 12 atoms in the chain, one or more of which is a heteroatom selected from S, O, and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, alkyl sulfides, and the like.

The term "alkenyl" refers to a straight- or branched-chain alkenyl group having from 2 to 12 carbon atoms in the chain. Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and the like.

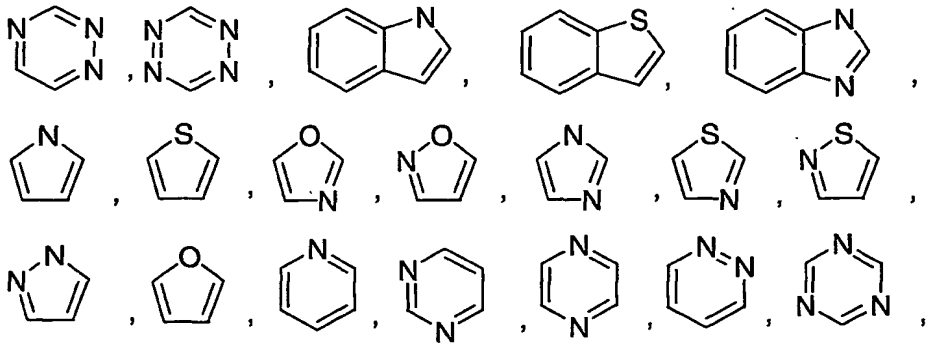
The term "alkynyl" refers to a straight- or branched-chain alkynyl group having from 2 to 12 carbon atoms in the chain. Illustrative alkynyl groups include prop-2-ynyl, but-2-ynyl, but-3-ynyl, 2-methylbut-2-ynyl, hex-2-ynyl, and the like.

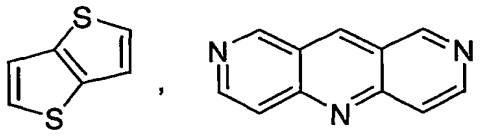
The term "aryl" (Ar) refers to a monocyclic, or fused or spiro polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12 ring atoms per ring. Illustrative examples of aryl groups include the following moieties:



, and the like.

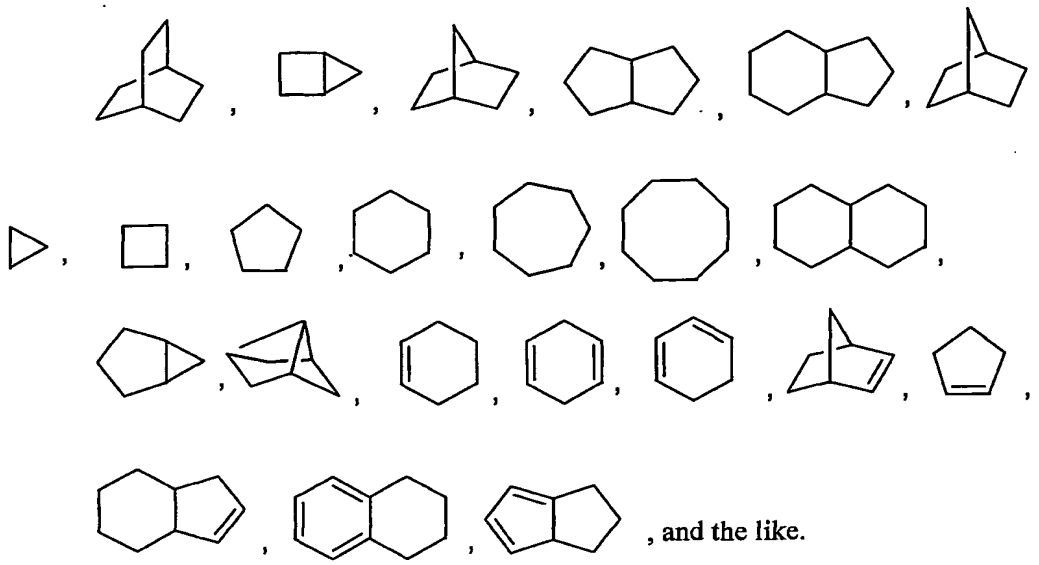
The term "heteroaryl" (heteroAr) refers to a monocyclic, or fused or spiro polycyclic, aromatic heterocycle (ring structure having ring atoms selected from carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per ring. Illustrative examples of aryl groups include the following moieties:





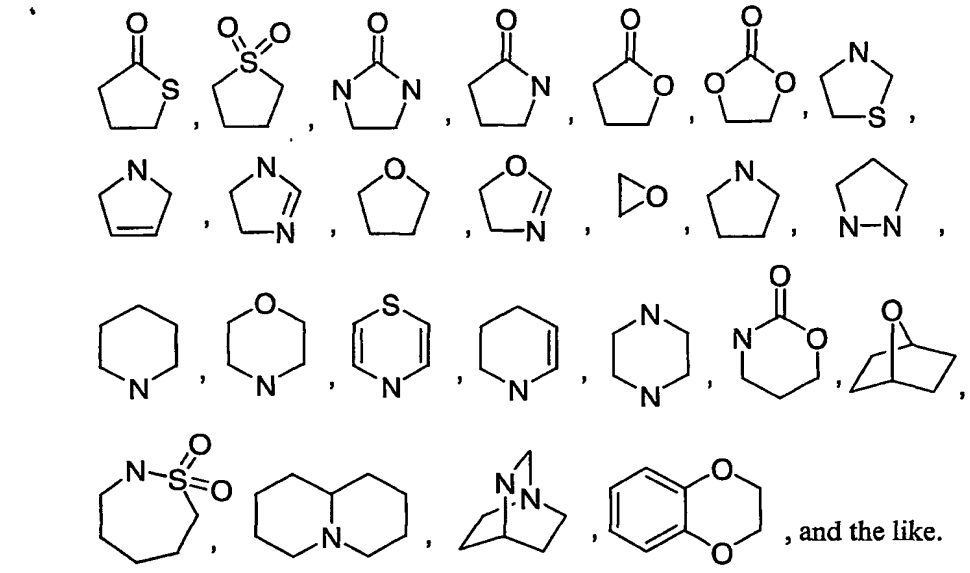
, and the like.

The term "cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle having from 3 to 12 ring atoms per ring. Illustrative examples of cycloalkyl groups include the following moieties:



, and the like.

A "heterocycloalkyl" refers to a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring selected from C atoms and N, O, and S heteroatoms. Illustrative examples of heterocycloalkyl groups include:



, and the like.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

Preferred GnRH agents of the invention include those having a K_i value of about 10 μM or less. Especially preferred GnRH agents are those having a K_i value in the nanomolar range.

It is understood that while a compound may exhibit the phenomenon of tautomerism, the formula drawings within this specification expressly depict only one of the possible tautomeric forms. It is therefore to be understood that a formula is intended to represent any tautomeric form of the depicted compound and is not to be limited merely to a specific compound form depicted by the structural formula.

It is also understood that a compound of Formula I, II or III may exist as an "E" or "Z" configurational isomer, or a mixture of E and Z isomers. It is therefore to be understood that a formula is intended to represent any configurational form of the depicted compound and is not to be limited merely to a specific compound form depicted by the formula drawings.

Some of the inventive compounds may exist as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. In one preferred embodiment, the inventive compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

As indicated above, GnRH agents in accordance with the invention also include active tautomeric and stereoisomeric forms of the compounds of Formula I, II or III, which may be readily obtained using techniques known in the art. For example, optically active (R) and (S) isomers may be prepared via a stereospecific synthesis, e.g., using chiral synthons and chiral reagents, or racemic mixtures may be resolved using conventional techniques.

Additionally, Formulas I, II, and III are intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

In addition to compounds of the Formulas I, II, and III, the GnRH agents of the invention include pharmaceutically acceptable salts, prodrugs, and active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites. Such non-peptide agents are pharmaceutically advantageous over peptide agents since they provide better biodistribution and tolerance to degradation by physiological enzymes.

A "prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound. An "active metabolite" is a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. See, e.g., Bertolini et al., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan et al., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, *Advances in Drug Res.*, 13, 224-331 (1984); Bundgaard, *Design of Prodrugs* (Elsevier Press 1985); and Larsen, *Design and Application of Prodrugs*, Drug Design and Development (Krogsgaard-Larsen et al. eds., Harwood Academic Publishers, 1991); Dear et al., *J. Chromatogr. B*, 748, 281-293 (2000); Spraul et al., *J. Pharmaceutical & Biomedical Analysis*, Vol. 3, No. 2, 103-112 (1992).

The term "pharmaceutically acceptable salts" refers to salt forms that are pharmacologically acceptable and substantially non-toxic to the subject being administered the GnRH agent. Pharmaceutically acceptable salts include conventional acid-addition salts or base-addition salts formed from suitable non-toxic organic or inorganic acids or inorganic bases. Exemplary acid-addition salts include

those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid, and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, methanesulfonic acid, ethane-disulfonic acid, isethionic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, 2-acetoxybenzoic acid, acetic acid, phenylacetic acid, propionic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, ascorbic acid, maleic acid, hydroxymaleic acid, glutamic acid, salicylic acid, sulfanilic acid, and fumaric acid. Exemplary base-addition salts include those derived from ammonium hydroxides (e.g., a quaternary ammonium hydroxide such as tetramethylammonium hydroxide), those derived from inorganic bases such as alkali or alkaline earth-metal (e.g., sodium, potassium, lithium, calcium, or magnesium) hydroxides, and those derived from organic bases such as amines, benzylamines, piperidines, and pyrrolidines.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystal or

polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

A variety of known assays and techniques may be employed to determine the level of activity of various forms of the compounds in the GnRH system. Ligand-binding assays are used to determine interaction with the receptor of interest. Where binding is of interest, a labeled receptor may be used, where the label is a fluorescer, enzyme, radioisotope, or the like, which registers a quantifiable change upon the binding of the receptor. Alternatively, the artisan may provide for an antibody to the receptor, where the antibody is labeled, which may allow for amplification of the signal. Binding may also be determined by competitive displacement of a ligand bound to the receptor, where the ligand is labeled with a detectable label. Where agonist and/or antagonist activity is of interest, an intact organism or cell may be studied, and the change in an organismic or cellular function in response to the binding of the compound of interest may be measured. Various devices are available for detecting cellular response, such as a microphysiometer available from Molecular-Devices, Redwood City, California. *In vitro* and *in vivo* assays useful in measuring GnRH antagonist activity are known in the art. See, e.g., Bowers et al., "LH suppression in cultured rat pituitary cells treated with 1 ng of LHRH," *Endocrinology*, 1980, 106:675-683 (*in vitro,*) and Corbin et al., "Antiovulatory activity (AOA) in rats," *Endocr. Res. Commun.*, 2:1-23 1975.. Particular test protocols that may be used are described below.

For example, GnRH-receptor antagonists may be functionally assessed by measurement of change in extracellular acidification rates as follows. The ability of compounds to block the extracellular rate of acidification mediated by GnRH in HEK 293 cells expressing human GnRH receptors is determined as a measure of the compound's antagonist activity *in vitro*. Approximately 100,000 cells/chamber are immobilized in agarose suspension medium (Molecular Devices) and perfused with unbuffered MEM media utilizing the Cytosensor® Microphysiometer (Molecular Devices). Cells are allowed to equilibrate until the basal acidification rate remains stable (approximately one hour). Control dose-response curves are performed to GnRH (10^{-11} M to 10^{-7} M). Compounds are allowed to incubate 15 minutes prior to stimulation with GnRH, and are assessed for antagonist activity. After incubation with test compounds, repeat dose-response curves to GnRH in the presence or absence of various concentrations of the test compounds are obtained. Schild

regression analysis is performed on compounds to determine whether compounds antagonize GnRH-mediated increases in extracellular acidification rates through a competitive interaction with the GnRH receptor.

In another test, accumulation of total inositol phosphates may be measured by formic acid extraction from cells, followed by separation of the phosphates on Dowex columns. Cells are split using trypsin into two 12-well plates and pre-labeled with ^{3}H-myoinositol (0.5 Ci to 2 mCi per mL) for 16-18 hours in inositol-free medium. The medium is then aspirated and the cells rinsed with either 1X HBSS, 20 mM HEPES (pH 7.5), or serum-free DMEM, 1X HBSS, 20mM HEPES (pH 7.5) containing test compound, and 20 mM LiCl is then added and the cells are incubated for the desired time. The medium is aspirated and the reaction stopped by addition of ice-cold 10 mM formic acid, which also serves to extract cellular lipids. Inositol phosphates are separated by ion-exchange chromatography on Dowex columns, which are then washed with 5 mL of 10 mM myoinositol and 10 mM formic acid. The columns are then washed with 10 mL of 60 mM sodium formate and 5 mM borax, and total inositol phosphates are eluted with 4.5 mL 1M ammonium formate, 0.1M formic acid.

It will be appreciated that the actual dosages of the agents of this invention will vary according to the particular agent being used, the particular composition formulated, the mode of administration, and the particular site, host, and disease being treated. Optimal dosages for a given set of conditions may be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for a given compound. For oral administration, an exemplary daily dose generally employed will be from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals. Administration of prodrugs may be dosed at weight levels that are chemically equivalent to the weight levels of the fully active compounds.

To treat diseases or conditions mediated by GnRH agonism or antagonism, a pharmaceutical composition of the invention is administered in a suitable formulation prepared by combining a therapeutically effective amount (i.e., a GnRH modulating, regulating, or inhibiting amount effective to achieve therapeutic efficacy) of at least one GnRH agent of the invention (as an active ingredient) with one or more pharmaceutically suitable carriers, which may be selected from diluents, excipients and auxiliaries that facilitate processing of the active compounds into the final

pharmaceutical preparations. Optionally, one or more additional active ingredients, such as a second GnRH agent, may be employed in a pharmaceutical composition according to the invention.

The pharmaceutical carriers employed may be either solid or liquid. Exemplary solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the inventive compositions may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate or the like. Further additives or excipients may be added to achieve the desired formulation properties. For example, a bioavaliability enhancer, such as Labrasol, Gelucire or the like, or formulator, such as CMC (carboxymethylcellulose), PG (propyleneglycol), or PEG (polyethyleneglycol), may be added. Gelucire®, a semi-solid vehicle that protects active ingredients from light, moisture and oxidation, may be added, e.g., when preparing a capsule formulation.

If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension. If a semi-solid carrier is used, the preparation may be in the form of hard and soft gelatin capsule formulations. The inventive compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent may be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3 M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I, II, or III is dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of

the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as

fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For administration to the eye, a GnRH agent may be delivered in a pharmaceutically acceptable ophthalmic vehicle such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, including, for example, the anterior chamber, posterior chamber, vitreous body, aqueous humor,

vitreous humor, cornea, iris/cilary, lens, choroid/retina and selera. The pharmaceutically acceptable ophthalmic vehicle may be an ointment, vegetable oil, or an encapsulating material. A compound of the invention may also be injected directly into the vitreous and aqueous humor.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD: 5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. The proportions of a co-solvent system may be suitably varied without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

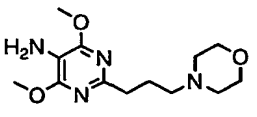
Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater

toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The compounds of Formulas I, II and III and their intermediates may be prepared by advantageous processes described below. Preferred intermediates useful for synthesizing the inventive compounds include 5-(2-methylphenoxy)-2-furoic acid, 5-[2-bromo-5-(tert-butyl)phenoxy]-2-furoic acid, 5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furoic acid, 5-(4-chloro-5-isopropyl)-2-methylphenoxy)-2-furoic acid, 5-[(4-bromo-3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furoic acid, and 6-methyl-2-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-4-pyrimidinecarboxylic acid. Additional preferred nitro and amine intermediates useful for synthesizing of GnRH agents of the present invention are: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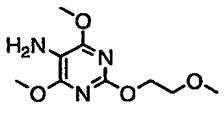
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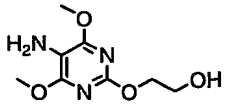
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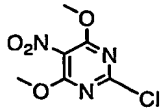
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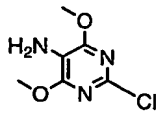
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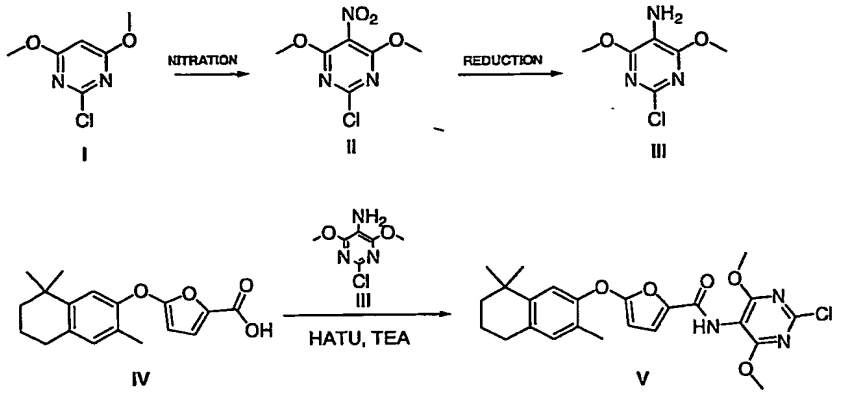
Methods for electrophilic aromatic nitration are described in the art. See, for example, Coon et al., *J. Org. Chem.*, 38: 4243 (1973); Yarbro et al., *J. Fluorine*

Chem. 6:187 (1975); Hakimelahi et al., *Hel. Chim. Acta* 61: 906 (1984); Suri et al., *Synthesis* 743(1988); Umenoto et al, *Tetrahedron Lett.* 31:3579 (1990); Shackelford et al., *Abstracts of the 11th Rocky Mountain Regional American Chemical Society Meeting*, Albuquerque, NM, July 10-12, 1992; and Adams et al., *Tetrahedron Lett.* 34: 6669 (1993). These methods have drawbacks, however. For example, the Yarbro et al. and Hakimelahi et al. methods generate anhydrous nitronium triflate using toxic, gaseous nitryl chloride, NO_2Cl, and corrosive triflic chloride (acid chloride).

Various drawbacks of prior methods have been overcome by the nitration process of the present invention, which comprises forming a nitrating reagent by adding trifluoromethanesulfonic anhydride to 2-tetramethylammonium nitrate in a polar solvent and reacting the nitrating reagent with an aryl or heteroaryl compound.

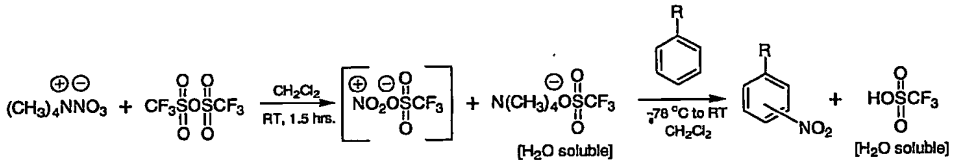
Advantages of the present method are, e.g.: a) simplified and more rapid aqueous work-up, thereby eliminating chromatographic column separation and/or plug filtration; b) improved reactant solubility and reduced byproduct formation as a result of organic solvents rather than aqueous or easily hydrolyzed, corrosive anhydride solvents; c) facilitated synthesis of regioisomeric nitrated products sometimes not available when using other nitration procedures; d) enables the preparation of novel nitroaromatic and nitroheterocyclic compounds; e) achieves selective and exclusive mono-nitration from mild reaction conditions; f) provides higher product yields than many conventional nitration procedures; g) higher crude nitrated product purity; and h) scaleable over a wide range to provide small or large product quantities.

This nitration method described herein may be used to provide nitrated benzene derivatives (e.g., Compound **II**) and aromatic heterocyclic intermediates. Such nitrated intermediates are reduced (e.g., Compound **II** to Compound **III**) to provide intermediates useful for preparing final GnRH agents of the invention (e.g., Compound **V**--the compound of Example **B52**).



I II III IV V

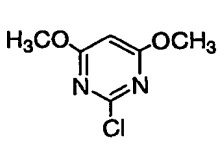
General Procedure for the Tetramethylammonium Nitrate-Generated Nitronium Triflate Nitration of Aromatic Compounds (General Procedure):



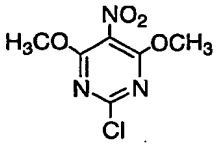
Under nitrogen at room temperature, 2.26–2.39 g trifluoromethanesulfonic anhydride was added dropwise from a pressure-equalized addition funnel to a stirred suspension of 1.12 g tetramethylammonium nitrate (96%) in 20 mL commercial anhydrous (or low water) dichloromethane (DCM) with a slight temperature rise resulting. The addition funnel was rinsed with 8 mL anhyd. DCM, and this rinse was added to the reaction suspension. After stirring for at least 1.5 hours, the stirred suspension was cooled in a dry ice/acetone bath to at least –69°C. The aromatic substrate, 7.50 mmol of in 10 mL DCM, was added dropwise to the stirred nitronium triflate suspension keeping the reaction temperature at –65.0°C or less. The addition funnel was then rinsed with 2 mL anhyd. DCM; this rinse also was added to the stirred reaction suspension. The dry ice/acetone bath could then be removed; however, many reactions proceeded more cleanly if the bath was kept in place 30 to 60 minutes and was then allowed to warm unattended to room temperature over the next 15 to 48 hours. In several reactions, the acetone bath was kept in place one hour and then was replaced with a dry ice/acetonitrile cold bath. The reaction was quenched by adding 15 mL of 5% sodium bicarbonate solution and stirring until bubbling ceased with an aqueous layer pH = 8 (With acidic compounds containing phenolic and carboxylic acid groups, only water was added to maintain an acidic pH).

The reaction contents were transferred with 25 mL DCM and 50 mL H_2O. The lower DCM layer was separated and washed with 5 x 25 mL H_2O. The combined H_2O washes were back-extracted with 25 ml DCM, and the combined DCM portions dried over anhyd. $MgSO_4$. DCM removal by rotary evaporation gave crude product. This procedure proportionally can be scaled to larger quantities by directly increasing reactant and solvent amounts while keeping reaction time periods the same.

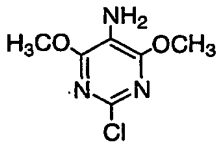
Compound **II**, shown below, was obtained in 98% crude yield with an isolated 99% crude product purity from reactant **I**. Originally synthesized on a 7.5 mmole scale, its synthesis has been scaled up to 2864 mmoles, again, with a resultant 98% crude product yield. One preliminary attempt to synthesize Compound **II** by the traditional HNO_3/acetic anhydride solvent procedure was not successful.



I



II

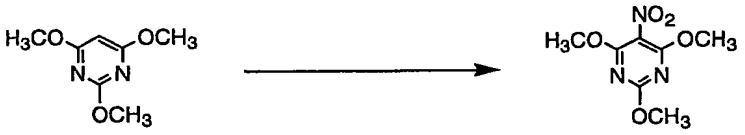


III

2-chloro-4,6-dimethoxy-5-nitropyrimidine (Compound II): Reacted 1.31g (7.50mmol) **I** with 1.50 equivalents of nitronium triflate for 48 hours at room temperature to obtain 1.61g **II**, (98%). FW = 219.6; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 6H); GC/MS (CI, *m/z*) 220 (M^+ and base peak); FTIR (KBr) 3126, 3073, (aromatic CH); 3000, 2958, 2924, 2852 (aliphatic CH); 1524, 1354, (NO_2), cm^{-1}; mp uncorrected = 131.8 to 132.0 °C; Elem. Anal. for $C_6H_6ClN_3O_4$ (crude product) calculated C 32.82%, H 2.75%, N 19.14%, Cl 16.15, found C 33.12 %, H 2.81%, N 18.95%, Cl 16.43.

2-chloro-4,6-trimethoxypyrimidin-5-amine (Compound III): A 500 mL three-necked, round bottom flask containing a Teflon-coated magnetic stirring bar and a thermometer was charged with 10.00 g (45.54 mmol) 2-chloro-4,6-dimethoxy-5-nitropyrimidine, 100 mL 190 proof ethanol, and 50 mL saturated, aqueous ammonium chloride solution. The resultant suspension was stirred at room temperature for several minutes while iron powder (-325 mesh) was added in several portions over a 22 minute period such that the reaction temperature from a slow rising exotherm did not exceed 56 °C. After addition of all the iron powder, the reaction was stirred for two and one-half hours in a room temperature environment. The reaction suspension was suction filtered, and the isolated iron powder was washed with 2 x 25 mL of

ethanol, followed by 3 x 25 mL of ethyl acetate. Too the organic filtrate was added 200 mL water and 50 mL more ethyl acetate to effect separation. The upper organic layer was separated, and the lower aqueous layer was extracted with 3 x 50 mL of ethyl acetate. All ethyl acetate portions were combined and dried over anhydrous magnesium sulfate. Suction filtration, washing the spent magnesium sulfate with 15 mL ethyl acetate, and rotary evaporation left a pinkish, wet solid. The wet solid was dissolved in 75 mL dichloromethane, and the dichloromethane was washed with 3 x 25 mL of water. The combined water washings were back-extracted with 25 mL dichloromethane. The combined dichloromethane portions were dried over anhydrous magnesium sulfate. Suction filtration, washing the spent magnesium sulfate with 25 mL dichloromethane, and rotary evaporation afforded 8.21 g (95%) of a cream-colored solid shown to be 98% pure by HPLC analysis. The NMR and mass spectrometry data consistent with the desired product is as follows: FW = 189.6; ^{1}H NMR (DMSO-d_6) δ 4.59 (s, 2H), 3.89 (s, 6H); FI/MS (APCI, *m/z*) 192.0, 190.0 (M^++1); FTIR (ATR film) 3420, 3342, 3290 (NH) 3180, 3010, (aromatic CH); 2960, 2871 (aliphatic CH); 1587, 1488, 1458, 1398, 1375, 1314, 1197, 1067, 942 (fingerprint) cm^{-1} ; Elem. Anal. for $C_6H_8ClN_3O_2$ calculated: C 38.01%, H 4.25%, Cl 18.70, N 22.16%, found C 38.24 %, H 4.32%, Cl 18.70, N 22.09%.

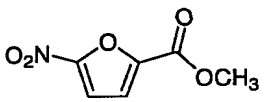


VI VII

The synthesis of **VII** was also achieved by direct nitronium triflate nitration of **VI** in a 73% crude yield with 85% crude yield purity. This represents the first synthesis of **VII** by direct nitration. Use of the acetic anhydride/nitric acid nitration procedure gave several byproducts plus **VII** in only 16% purity. The only other literature preparation appearing in the Beilstein electronic data base for **VII** produced it from **VI** and gave a 66% yield [Cherkasov, V. M.; Remennikov, G. Ya.; Kisilenko, A. A. *Chem. Heterocycl. Compd.* (Engl. Transl.); EN; 526 (1982)].

2,4,6-trimethoxy-5-nitropyrimidine (Compound VII): Into a 5-L three-necked, round bottom flask fitted with an overhead mechanical stirrer, was placed 920 g (0.675 mole) of tetramethylammonium nitrate and 1 L DCM. The reaction flask was fitted with a thermometer and addition funnel. The suspension was stirred under

nitrogen gas for 15 minutes at room temperature. Into the addition funnel was placed 190 g (0.675 mole, 118mL) of trifluoromethanesulfonic anhydride that was added dropwise to the stirred suspension over a 35 minute duration so the temperature did not rise more than 5 °C. The addition funnel was rinsed with a small amount of DCM, and this rinse was added to the stirred reaction suspension. The resultant suspension was stirred at room temperature for 1.5 hours. The addition funnel was charged with 76.9 g (0.452 mole) dissolved in a minimum amount of DCM and was added dropwise at room temperature over 85 minutes such that the reaction temperature did not rise more than 5 °C, and a bright crimson red suspension resulted. The reaction was stirred overnight at room temperature. Work up entailed adding 5 kg of ice to the stirred reaction suspension followed by 10% $NaHCO_3$ solution until a pH 8 was reached and the reaction turned from a burgundy to purple to blue to green to yellow color change. The lower DCM layer was separated and washed with 3 x 1.5 L of water. The DCM portion was then dried sodium sulfate, filtered, and the DCM solvent was removed by rotary evaporation giving *ca.* 70 g of green solid. Recrystallization from methanol/water in two crops afforded 50.5 g of purified product for an overall 52% yield. The NMR and mass spectrometry data consistent with the desired product is as follows: FW = 215.2; ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 6H), 4.02 (s, 3H); FI/MS (APCI, *m/z*) 216 (M^++1 and base peak); FTIR (ATR film) 3047, 3009, 2999 (aromatic CH); 2957, 2877, 2847 (aliphatic CH); 1578, 1338 (NO_2), cm^{-1}; Elem. Anal. for $C_7H_9N_3O_5$ calculated: C 39.07%, H 4.22%, N 19.53%, found C 39.14 %, H 4.19%, N 19.61%.

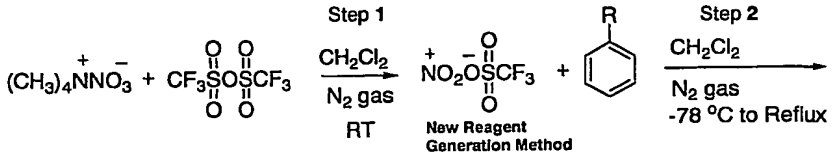


VIII

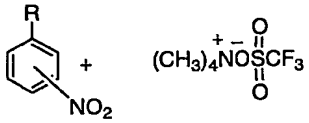
Compound **VIII** represents another class of aromatic heterocycle product that was obtained by the above mentioned nitronium triflate method and demonstrates that a pendant ester group also is not attacked nor modified by these nitration conditions.

Anhydrous, Electrophilic, Aromatic Nitration with Tetramethylammonium Nitrate:

Nitration of non-heterocyclic aromatic compounds are also achieved with this anhydrous, one-pot, two-step method in which the nitronium triflate **XVI** nitrating reagent is generated *in-situ* under a static nitrogen gas blanket from tetramethylammonium nitrate **XIV** and trifluoromethanesulfonic anhydride (triflic anhydride) **XV**. The aromatic compound to be nitrated is then introduced **XVII**. Nitration occurs to produce the desired product **XVIII** plus the tetramethylammonium tiflate salt byproduct **XIX**.



XIV **XV** **XVI** **XVII**



XVIII **XIX**

When using the tetramethylammonium nitrate reagent **XIV**, the resulting salt byproduct **XIX** is water soluble and is removed during an aqueous work-up leaving only the desired nitrated product **XVIII** after drying. Under similar reaction conditions, higher homologues of **XIV** (*e.g.* tetra-*n*–butylammonium nitrate and tetraethylammonium nitrate) require additional, time intensive purification by column chromatography or short column Silica Gel filtration to remove the analogous **XIX** byproduct. The one lower homolog, ammonium nitrate, gives irreproducible results under analogous nitration conditions.

Most reactions have been conducted in methylene chloride solvent at room temperature. However, chloroform, dichloroethane, and nitromethane also would be suitable solvents and would permit higher temperatures to be achieved by refluxing the reaction in step 2 with electron-deficient aromatic ring systems or when attempting to effect aromatic dinitration.

From 1.05 to 1.50 equivalents of nitronium triflate have been used for mononitration of the aromatic or heterocyclic reactant with excess reagent having no deleterious effect. The less reactive the reactant, the larger the excess of nitronium

triflate is needed for complete conversion. More than 1.5 equivalents of nitronium triflate could be used; no upper limit has been determined.

This reaction method (General Procedure) has been scaled linearly from the 7.5 mmole size (aromatic compound to be nitrated) to 92.9 mmoles. To date, no upper limit has been established. It appears this method is limited only by the size of equipment available.

Additional Nitration Examples:

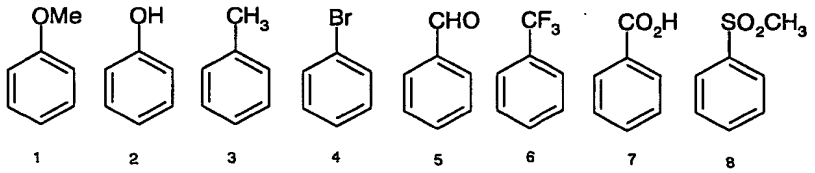
The following mono-substituted benzene compounds were evaluated for directing effects and substituent stability during the reaction conditions of this nitration method (ND = not detected). Table 1 illustrates the wide scope of mono-substituted benzenes nitrated with this method and reveals the directional susceptibility of nitronium triflate nitration to aromatic pendant group effects. The nitrations were conducted with 1.05 equivalents of nitronium triflate as described by the General Procedure. Reaction conditions were not optimized for these exploratory reactions, and isomeric percentages were determined by proton NMR analysis of the isolated crude products.

Table 1. Tetramethylammonium Nitrate Nitration of Mono-Substituted Benzenes (7.5 mmol scale).

Compound	No.	Conversion (%)	Isolated Yield (%)	*o/m/p*-Isomers (%)	Time (hrs.)
R = OCH_3	**1**	100	97	63/5/32	24
OH	**2**	100	74	90/0/10	23
CH_3	**3**	100	99	62/0/38	24
Br	**4**	95	90	33/0/67	26
CHO	**5**	ND	70	31/63/6	97
CF_3	**6**	ND	68	8/88/4	24
----	**6**	---	68	7/89/4	48
COOH	**7**	71	52	13/78/6	26
SO_2CH_3	**8**	57	89[A]	13/84/3	102

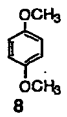
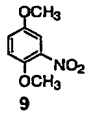
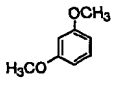
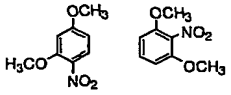
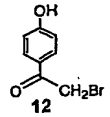
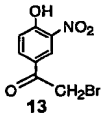
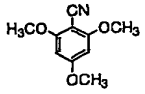
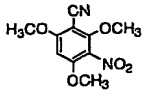
ND = not determined because of reactant volatility and its loss during solvent removal.

A= Actual yield in a pure isolated mixture contained only reactant (43%) and product isomers (57%).



This one-pot tetramethylammonium nitrate-based nitration also was applied to multiple-substituted aromatic compounds under the same reaction conditions. Table 2 displays the results obtained.

Table 2. Tetramethylammonium Nitrate Nitration of Multiple-Substituted Benzenes (7.5 mmol scale).

Compound	% Converted	Product(s)	Reaction Time	Isolated Yield (%)	Isolated Purity (%)
 **8**	100 %	 **9**	17 hrs.	71%	92%
 **10**	100 %	 95% **11a** 5% **11b**	15 hrs.	82%	—
 **12**	100 %	 **13**	27 hrs.	94%	91%
 **14**	58 %[A] 96 %[A] 100 %[B]	 **15**	15 hrs. 46 hrs. 53 hrs.	43% 80 % 82%	— 81% 95%

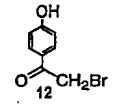
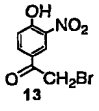
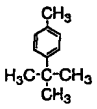
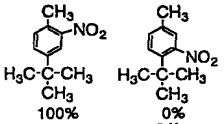
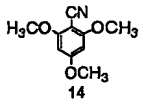
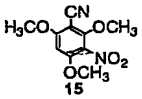
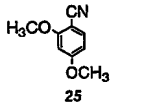
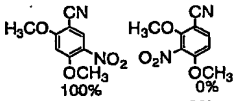
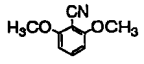
A. NO_2OTf equivalents = 1.05 relative to the reactant **14**.
B. NO_2OTf equivalents = 1.50 relative to the reactant **14**.

Compound purity was determined by HPLC analysis. Crude product **9** was purified further by preparative HPLC to greater than 99%. Compound **13** was purified by recrystallization from hexane. Both **9** and **13** gave acceptable elemental analyses. The only previous synthesis of **13** by direct nitration used fuming nitric acid at 5 °C for one hour, and gave a 70% crude product yield with an apparent purification obtained from an ethanol recrystallization as described by Garg et al., *J. Chem. Soc.*, 607, (1969). Compound **10** and its products **11a** and **11b** reveal that the sterically crowded position between 1,3-disubstituted methoxy groups is not attacked when less sterically hindered positions are available. When no alternative is available, nitration readily occurs between two 1,3-di-substituted methoxy groups as shown by 2,4,6-trimethoxybenzonitrile **14** where product **15** is obtained in good yield and purity. Other than the equivalents of NO_2OTf, used, the main difference in reaction conditions between the latter two runs of reactant **14** was reactant **14** had a slower warming profile that gave the highest crude yield and purity for product **15**. In the first two reactions with **14**, the dry ice/acetone

cooling bath was removed immediately after adding reactant **14** like that described in the General Procedure. The better result in the third reaction of **14** was obtained by replacing the dry ice/acetone cooling bath with a dry ice/acetonitrile cooling bath for 2.5 hours (-50°C to –35°C), allowing the bath to warm to 9°C over the next 2.5 hours, then removing the cooling bath completely and stirring the reaction for 48 hours. Product **15** has not previously been reported in the chemical literature and represents a new compound.

This General Procedure scales directly from 7.5 to 100 millimoles by proportionally increasing the amounts of reagent and solvent while keeping reaction times the same. Results of large-scale reactions appear in Table 3. Unless stated otherwise, product particles were determined by HPLC analysis.

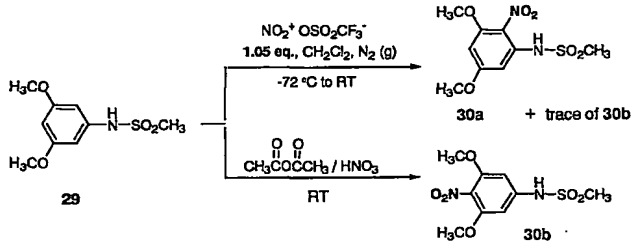
Table 3. Tetramethylammonium Nitrate Nitration at Large-Scale (86 to 100 mmol scale).

Reactant	Scale	Equiv. of 3	Product(s)	Reaction Time	Isolated Yield	Isolated Purity
 **12**	93 mmoles	1.1	 **13**	23 hrs.	91%	88% (nmr)
 **23**	86 mmoles	1.05	 100% **24a** 0% **24b**	24 hrs.	94%	93% (nmr)
 **14**	90-100 mmoles	1.5-1.7	 **15**	48-52 hrs.	82-84%	90-95%
 **25**	100 mmoles	1.5	 100% **26a** 0% **26b**	52 hrs.	91-96%	78-82%
 **27**	100 mmoles	1.5	 **28**	48-52 hrs.	100%	97%

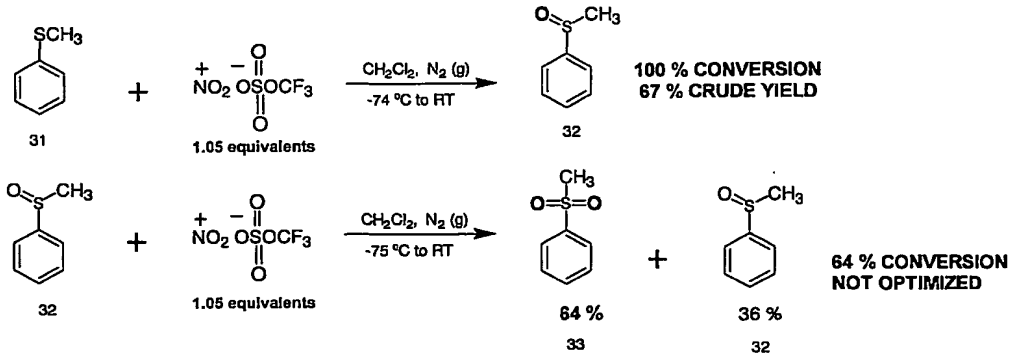
As shown in Tables 2 and 3, the brominated acetyl group of reactant **12** was stable to the mild nitronium triflate electrophilic nitration conditions. The carbonyl group in aldehyde, and carboxylic actid groups are compatible with this nitration procedure (Table 1), as is an ester group, and the unsaturated cyano group is compatable with this reaction.

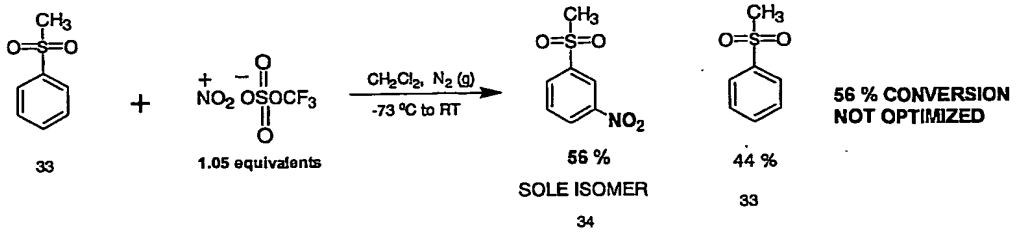
In the smaller 7.5 milligram scale nitration of reactant **10**, nine percent of product isomer **11b** was obtained and was removed by recrystallization. No formation of product **11b** was obtained in the larger scale reaction, see Table 3. Compound **23** selectively produced the one isomeric product **24a** in an excellent yield. In contrast, a literature nitration of **23** using the nitronium tetrafluoroborate reagent (NO_2^+ BF_4^-) produced 5% **24b** by product as an impurity as described in Olah et al, *J. Am. Chem. Soc.*, 86, 1067, (1964).

Compound **29** nitrated by this method gave different results when compared with the standard acetic anhydride/nitric acid nitration system. Each method gave the different regioisomer in exclusive or a nearly exclusive yield. The nitronium triflate method heavily favored *ortho*-nitration with respect to the methylsulfamide group **30a**, while the standard acetic anhydride/nitric acid method provided exclusive *para*-nitration **30b.**

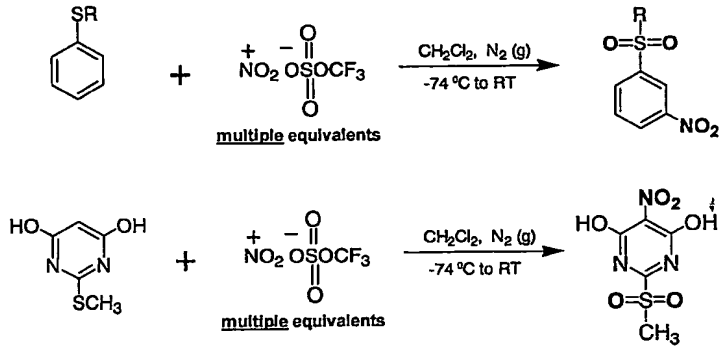


In the oxidative environment of this *in-situ* nitration method, aromatic alkylsulfides **31** are cleanly oxidized to their analogous sulfoxide **32**, and the sulfoxide **32** is then oxidized to a sulfone **33** in an apparent stepwise fashion. Once the fully oxidized sulfone **33** is obtained, nitration can then occur to provide the mono-nitrated sulfone **34**. This is illustrated by the three following non-optimized reactions.





In each reaction step, only the product and unconverted reactant were detected with no byproducts present. With the correct number of nitronium triflate equivalents, unique aromatic sulfones could be made during a clean, one-pot reaction.



The nitrated products obtained by this nitration method shown in Tables 2 and 3 were characterized as follows:

1,4-Dimethoxy-2-nitrobenzene (9): Reacted 1.04 g (7.50 mmol) **8** with 1.05 equivalents of nitronium triflate to obtain an isolated yield of 0.97 g (71%). FW = 183.1; ^{1}H NMR (DMSO-d_6) δ 7.46 (s, 1H), 7.28 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H). GC/MS (CI, *m/z*) 183 (M^+ and base peak); FTIR (KBr,) 3071, 3024 (aromatic CH), 2982, 2946, 2844 (aliphatic CH), 1528, 1355 (NO_2) cm^{-1}; mp uncorrected, (crude = 68.6 to 70.0°C), (hplc purified = 70.8 to 71.2 0 °C), lit. mp = 71-73°C, 68-70 °C, 71 °C; Elem Anal for $C_8H_9NO_4$ calcd C 52.46%, H 4.95%, N 7.65%, found C 52.55%, H 4.94%, N 7.63.

1,3-Dimethoxy-4-nitrobenzene (11a): Reacted 1.04 g (7.50 mmol) **10** with 1.05 equivalents of nitronium triflate to obtain an isolated yield of 1.13 g (82% with 5% **11b** isomer). FW = 183.1; ^{1}H NMR (DMSO-d_6) δ 7.97 (d, J = 9Hz, 1H), 6.80 (d, J = 2Hz, 1H), 6.67 (dd, J_1 = 9Hz, J_2 = 3Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H); GC/MS (CI, *m/z*) 183 (M^+ and base peak).

1,3-Dimethoxy-2-nitrobenzene (11b): FW = 183.1; ^{1}H NMR (DMSO-d_6) δ 7.48 (t, 1H), 6.89 (d, 2H), 3.86 (s, 6H); GC/MS, (CI, *m/z*) 183 (M^+ and base peak).

2-Bromo-1-(4-hydroxy-3-nitrophenyl)ethanone (13): Small Scale: Reacted 1.70 g (97.91 mmol) **12** with 1.15 equivalents of nitronium triflate to obtain an

isolated yield of 1.93 g (93%). Large Scale: Reacted 19.98 g **12** with 1.10 equivalents of nitronium triflate to obtain an isolated yield of 21.90 g (91%). Recrystallized from hot hexane. FW = 260.0; ^{1}H NMR (DMSO-d_6) δ 12.18 (brd. s, 1H), 8.49 (s, 1H), 8.13 (d, 1H), 7.24 (d, 1H), 4.89 (s, 2H); ES/MS (CI, *m/z*) 260 (M^+), 258 (base peak); FTIR (KBr) 3279 (OH), 3086, (aromatic CH); 2997, 2940 (aliphatic CH), 1695 (C=O), 1568, 1329 (NO_2) cm^{-1}; mp uncorrected = 87.8 to 89.4 °C, (lit. mp = 91.5 to 92.0°C), Elem Anal for $C_8H_6BrNO_4$ calcd C 36.95%, H 2.33%, N 5.39%, Br 30.73%, found, C 37.28 %, H 2.34%, N 5.44%, Br 30.90%.

2,4,6-Trimethoxy-3-nitrobenzonitrile (15): Small Scale: Reacted 1.48 g (7.51 mmol) **14** (98%) with 1.50 equivalents of nitronium triflate to obtain an isolated yield of 1.54 g (86%). Large Scale: Reacted 17.80 g (90.29 mmol) **14** (98%) with 1.66 equivalents of nitronium triflate to obtain an isolated yield of 17.59 g (82%). Recrystallized from methanol. FW = 238.2; ^{1}H NMR (DMSO-d_6) δ 6.79 (s, 1H), 4.02 (s, 6H), 4.01 (s, 1H); FI/MS (APCI, *m/z*) 209 (M^+-30 and base peak); FTIR (ATR film) 3114, (aromatic CH); 2994, 2957, 2924, 2984 (aliphatic CH), 2228 (CN), 1529, 1349 (NO_2) cm^{-1}; mp uncorrected = 195.2 to 195.6 °C; Elem Anal for $C_{10}H_{10}N_2O_5$ calcd C 50.42%, H 4.23%, N 11.76%, found C 50.60 %, H 4.18%, N 11.80%.

4-*tert*-Butyl-2-nitrophenol (24a): FW = 193.3; Reacted 12.2 g (82.3 mmol) **23** with 1.04 equivalents of nitronium triflate to obtain an isolated yield of 15.0 g (94%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.40 (d, 1H), 7.12 (d, 1H), 2.42 (s 3H), 1.21 (s, 9H); GC/MS (CI, *m/z*) 194 (M^++1), 178 (base peak).

2,4-Dimethoxy-5-nitrobenzonitrile (26a): Small Scale: Reacted 1.23 g (7.54 mmol) **25** (98%) with 1.25 equivalents of nitronium triflate to obtain an isolated yield of 1.40 g (89% with 9% **26b** isomer). Large Scale: Reacted 16.65 g (100.0 mmol) **25** (98%) with 1.50 equivalents of nitronium triflate to obtain an isolated yield of 18.99 g (91%). Recrystallized from methanol. FW = 208.2; ^{1}H NMR (DMSO-d_6) δ 8.46 (d, J = 3Hz, 1H), 6.99 (s, J = 3Hz, 1H), 4.06 (s, 6H); GC/MS (CI, *m/z*) 208 (M^+), 161 (base peak); FTIR (ATR film): 3126, 3073 (aromatic CH) 3000, 2958, 2924, 2852, (aliphatic CH), 2232 (CN), 1524, 1354 (NO_2) cm^{-1}; mp uncorrected = 195.8 to 196.4 °C; Elem Anal for $C_9H_8N_2O_4$ calcd C 51.93%, H 3.87%, N 13.46%, found, C 51.93 %, H 3.85%, N 11.45%.

2,6-Dimethoxy-3-nitrobenzonitrile (28): Reacted 16.82 g (100.0 mmol) **27** (97%) with 1.50 equivalents of nitronium triflate to obtain an isolated yield of 20.85 g (100%). Recrystallized from methanol. FW = 208.2; ^{1}H NMR (DMSO-d_6) δ 8.34 (d, 1H), 7.18 (d, 1H), 4.03 (s, 6H); FI/MS (APCI, *m/z*) 209 (M^++1), 208 (M^+), 179 (base peak); GC/MS (CI, *m/z*) 208 (M^+), 178 (base peak); FTIR (ATR film) 3114 (aromatic CH), 2994, 2957, 2924, 2854 (aliphatic CH), 2228 (CN), 1529, 1349 (NO_2) cm^{-1}; mp uncorrected, crude = 115.4 to 115.6 °C); Elem Anal for $C_9H_8N_2O_4$ calcd C 50.42%, H 4.23%, N 11.76%, found C 50.60 %, H 4.18%, N 11.80%.

N-(3,5-dimethoxy-2-nitrophenyl)methanesulfonamide (30a): Reacted 1.75 g (7.51 mmol) **29** with 1.05 equivalents of nitronium triflate to obtain an HPLC purified yield of 0.25 g (11%). FW = 276.3; ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 6.88 (d, J = 3Hz, 1H), 6.32 (d, J = 3Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.03 (s 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) 164.01 (1C), 156.35 (1C), 134.75 (1C), 97.65 (1C), 96.45 (1C), 57.18 (1C), 56.47 (1C), 40.57 (1C); FI/MS (ANCI, *m/z*) 275 (M^--1).

N-(3,5-dimethoxy-4-nitrophenyl)methanesulfonamide (30b): Reacted 0.544 g (2.35 mmol) **29** with fuming nitric acid in acetic anhydride in an ice bath for 30 minutes, removed ice bath for 4 hrs, and worked up reaction to obtain an HPLC purified yield of 0.070 g (10%). FW = 276.3; ^{1}H NMR ($CDCl_3$) δ 6.48m (s, 2H), 6.87 (s, 6H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) 153.49 (2C), 140.26 (1C), 126.28 (1C), 95.85 (2C), 57.07 (2C), 40.12 (1C); FI/MS (APCI, *m/z*) 277 (M^++1).

Procedural Notes:

Reactant **14** (Table 2): the first two runs were conducted by removing the dry ice/acetone bath as described in the General Procedure. The best small-scale result with **14** used a slower warming profile by replacing the dry ice/acetone cooling bath with a dry ice/acetonitrile cold bath fro 2.5 hours (-49.6°C to –35.0°C), allowing the bath to warm to 9.0°C over the next 2.5 hours (-35.0°C-9.0°C), then removing the bath completely and stirring for 48 hours. This led to the following temperature warming modification for the large-scale nitrations with reactants **14**, **25**, and **27**. After addition of aromatic reactant, the reaction was kept one hour in the dry ice/acetone bath; then, it was then replaced with a dry ice/acetonitrile bath (*ca.* –45°C) for three hours, after which, the bath was permitted gradually to warm unattended to room temperature (RT) over the nexr 48 hours. For compound **23**, the dry ice/acetone bath was removed as soon as addition was complete and was stirred in a RT environment for 24 hours. For compound **12** (large scale), the dry ice/acetone bath was not removed following its addition, but was left in place to warm gradually, unattended to RT over the next 23 hours.

Synthesis Of GnRH Reagents And Compounds:

The inventive agents may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of preferred compounds of the present invention is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other protein kinase inhibitors of the invention. For example, the synthesis of non-exemplified compounds according to the invention may be

successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art. For example, the preparation of free amines from common salt forms and stock reagent solutions can be useful for small-scale reactions. See also Abdel-Magid *et al.*, "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride," *J. Org. Chem.* 61: 3849 (1996).

Methanolic solutions of the free bases can be prepared from hydrochloride, dihydrochloride, hydrobromide, or other salts when the free base is soluble in methanol. In this procedure, once the sodium methoxide is added, care should be taken to prevent exposure to air, since amine free bases, particularly primary amines, absorb carbon dioxide from the air to form salts. A 10-mL quantity of a 0.1M solution of a free base in methanol may be prepared as follows. Weigh 1.0 mmol of a monohydrochloride salt into a tared Erlenmeyer flask containing a stirring bar, and add 7 mL of methanol. To the stirred slurry, add 229 mL (1.0 mmol, 1 equiv.) of sodium methoxide in methanol (25 wt %, 4.37 M), stopper the flask, and stir the mixture vigorously for 2 hours. The slurry will sometimes change in appearance as a finer, milky precipitate of sodium chloride is formed. Filter the slurry through a 15-mL medium fritted glass funnel, wash the filter case with 1-2 mL methanol, transfer the filtrate to a 20-mL vial, and dilute to 10 mL with methanol. The theoretical yield of sodium chloride is nearly 59 mg, but the recovery is usually not quantitative, owing to a slight solubility in methanol. For a dihydrochloride salt, a second equivalent of sodium methoxide is required (458 mL).

A 0.5 M solution of sodium borohydride in ethanol may be prepared as follows. Sodium borohydride (520 mg, 13.8 mmol) is stirred in pure (non-denatured) anhydrous ethanol (25 mL) for ~2-3 minutes. The suspension is filtered through a medium fritted glass funnel to remove a small amount of undissolved solid (typically about 5% of the total mass of borohydride, or 25 mg). The filtrate should appear as a colorless solution that evolves only a little hydrogen. This solution should be used immediately, as it decomposes significantly over a period of a few hours, resulting in the formation of a gelatinous precipitate. Sodium borohydride is hygroscopic, so

avoid exposure to air by making the solution at once after weighing the solid. Sodium borohydride has a solubility of about 4% in ethanol at room temperature. This corresponds to a little over 0.8 M. However, sometimes a small percentage of the solid remains undissolved regardless of the concentration being prepared, even after stirring for $\geq$ 5 minutes.

Material and Methods:

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius and all parts and percentages are by weight, unless indicated otherwise.

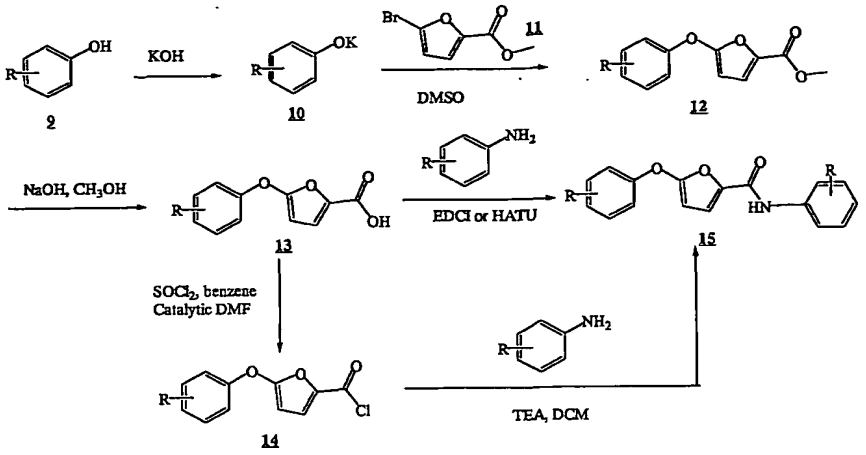
Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated. Tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were purchased from Aldrich in SureSeal® bottles and used as received. All solvents were purified by using standard methods in the art, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks are fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven-dried and/or

Exemplary GnRH Agents:

The following compounds were prepared according to Scheme A set forth below:

Scheme A



Potassium phenoxide 10: A mixture of potassium hydroxide (2.55g, 44.8 mmol) and the appropriate phenol 9 (52.9 mmol) was heated in an oil bath at 150-155 °C for 1-2 hours. The dark colored liquid was then evacuated at 130-140 °C to remove water. The residue (potassium phenoxide 10) was dried *in vacuo* overnight. Alternatively, the phenoxide 10 may be prepared by reaction with potassium t-butoxide in tetrahydrofuran.

Condensation 12: A mixture of potassium phenoxide 10 (7 mmol), prepared as described above, and methyl 5-bromo-2-furoate 11 (5.8 mmol) in DMSO (10 mL) was heated at 85 °C under nitrogen atmosphere. The reaction mixture was then diluted with water, and the aqueous mixture was acidified with concentrated HCl, and then extracted with diethyl ether. The combined ether extracts were concentrated and the product 12 was purified by silica gel chromatography, eluting with a mixture of ethyl acetate and hexanes (1:5 to 1:1 v/v). Yield was in the range of 50-80%.

Saponification 13: The methyl ester 12 obtained from above was dissolved in methanol (4 mmol in 15 mL of solvent). An aqueous solution of sodium hydroxide (0.7g in 5 mL water) was added. The mixture was monitored by TLC for completion of reaction. It was concentrated, diluted with water, and extracted with diethyl ether. The aqueous layer was then acidified with concentrated HCl, and extracted with ethyl acetate. The ethyl acetate extracts were washed with brine, dried over magnesium sulfate and concentrated to give a solid residue. The product 5-substituted-2-furoic acid 13 may be purified, if necessary, by silica gel chromatography. Yield was greater than 90%.

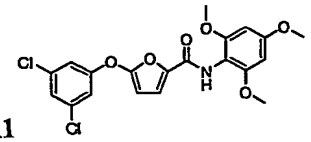
Amide Formation: Procedure 1: The furoic acid 13 from above (1 mmol) was dissolved in dimethylformamide (5 mL). To this solution was added 1-ethyl-3-(3-

dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 1 mmol), followed by the addition of the appropriate aniline or aniline hydrochloride (1 mmol), and triethylamine (1.1 mmol). The reaction mixture was stirred at room temperature overnight. DMF was removed on a rotovap. The residue was suspended in ethyl acetate, and washed with 10% HCl (aqueous), aqueous sodium bicarbonate, brine, and dried over magnesium sulfate. The solvent was removed on a rotovap. The product **15** was purified by silica gel chromatography using a mixture of ethyl acetate/hexanes (2/1 v/v) as the eluting solvent.

Procedure 2: The furoic acid **13** from above (1 mmol) was dissolved in dimethylformamide (5 mL). To this solution was added HATU (1 mmol), followed by the addition of the appropriate aniline or aniline hydrochloride (1 mmol), and triethylamine (2-3 mmol). The reaction mixture was stirred at room temperature overnight. DMF was removed on a rotovap. The residue was suspended in ethyl acetate, and washed with 10% HCl (aqueous), aqueous sodium bicarbonate, brine, and dried over magnesium sulfate. The solvent was removed on a rotovap. The product **15** was purified by silica gel chromatography using a mixture of ethyl acetate/hexanes (2/1 v/v) as the eluting solvent.

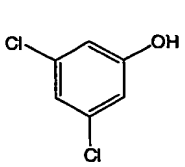
This procedure may be applied to the synthesis of anilides of the present invention. Alternatively, the appropriate amide **15** may be prepared via carboxylic acid chloride **14**. A suspension of **13** (300mmol) in anhydrous benzene (100ml) containing a ew drops of anhydrous DMF was heated to relux under nitrogen as thionyl chloride(1.1 eq.) in benzene (35ml) was added dropwise. The solution was refluxed for 10 hours and then cooled to room temperature and concentrated under vacuum to give **14**. A mixture of the appropriate aniline or aniline hydrochloride salt (1.2eq.) and triethylamine (2.5eq) in dichloromethane was stirred at 0°C under nitrogen as a solution of **14** in dichloromethane was added dropwise. The solution was allowed to warm to room temperatureand further stirred for 12 hours. The resulting suspension was washed several times with 2N hydrochloric acid, saturated soduim bicarbonate, brine and water successively. The organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum to give **15** which was then purified by column chromatography.

Example A1: 5-(3,5-dichlorophenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

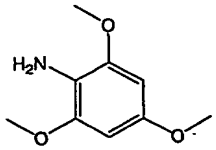


A1

Compound A1 was made according to Scheme A where:

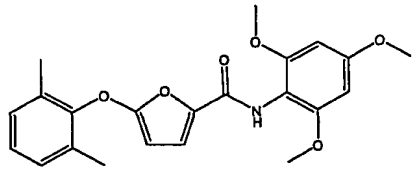


and



were used as the starting materials Yield of the purified product was 70-85%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 9H), 5.78 (d, 1H), 6.15 (s, 2H), 7.00 (s, 2H), 7.16 (d, 2H), 7.24 (s, 1H), APCI-MS *m/z* 438 $(M+H)^+$.

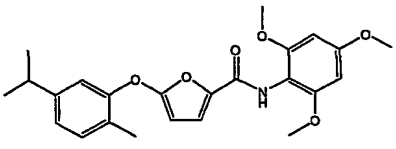
Example A2: 5-(2,6-dimethylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



A2

Compound A2 was synthesized in a manner analogous to that of A1, according Scheme A. Yield of the purified product was 17%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 6H), 3.83 (s, 3H), 3.85 (s, 6H), 4.96 (d, 1H), 6.20 (s, 2H), 7.05 (d, 1H), 7.10 (s, 3H), 7.20 (br s, 1H), APCI-MS *m/z* 398.1 $(M+H)^+$.

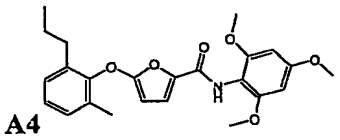
Example A3: 5-(5-isopropyl-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



A3

Compound A3 was synthesized in a manner analogous that of A1, according to Scheme A. The yield of the purified product was 48%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.26 (s, 3H), 2.88 (m, 1H), 3.81 (s, 9H), 5.38 (d, 1H), 6.18 (s, 2H), 6.95 (br s, 1H), 7.0 – 7.21 (m, 4H), APCI-MS *m/z* 426.1 $(M+H)^+$.

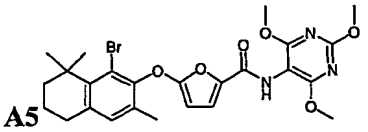
Example A4: 5-(2-methyl-6-propylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



A4

Compound A4 was synthesized in a manner analogous to that of A1, according to Scheme A. NMR data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.58 (sextet, 2H), 2.26 (s, 3H), 2.56 (t, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 4.96 (d, 1H), 6.18 (s, 2H), 7.10 (d, 1H), 7.13 (s, 3H), 7.22 (br s, 1H), APCI-MS *m/z* 426.1 $(M+H)^+$.

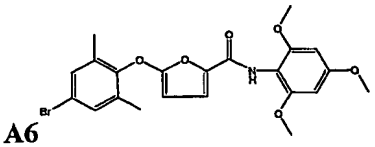
Example A5: 5-[(1-bromo-3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-N-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



A5

Compound A5 was synthesized in a manner analogous to that of A1, using similar starting compounds and where the pyrimidine is made from nitro compound VII which was further reduced to the amine in a manner analogous to that of compound III. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (CH3OD): δ 1.18 (s, 6H), 1.57 (d, 2H, J = 6.04 Hz), 1.77 (d, 2H, J = 6.42, 3.40 Hz), 2.27 (s, 3H), 2.68 (m, 2H, J = 6.80, 6.42 Hz), 3.86 (s, 6H), 3.91 (s, 3H), 5.32 (d, 1H, J = 3.40 Hz), 7.09 (d, 1H, J = 4.91 Hz), APCI-MS *m/z* 546 $(M+H)^+$.

Example A6: 5-(4-bromo-2,6-dimethylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

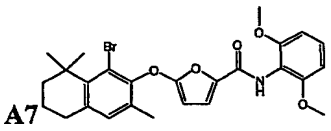


A6

Compound A6 was synthesized in a manner analogous to that of A1, according to Scheme A, via the acid chloride as set forth above. The yield of the purified product was 35%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 6H),

3.76 (s, 3H), 3.77 (s, 6H), 4.92 (d, 1H), 6.12 (s, 2H), 6.98 (d, 1H), 7.11 (br s, 1H), 7.19 (d, 2H), APCI-MS *m/z* 475.9 $(M+H)^+$.

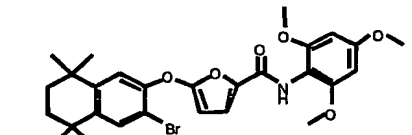
Example A7: 5-[(1-bromo-3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-N-(2,6-dimethoxyphenyl)-2-furamide



A7

Compound A7 was synthesized in a manner analogous to that of A1, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (CH_3OD): δ 1.18 (s, 6H), 1.56 (m, 2H), 1.78 (m, 2H), 2.28 (s, 3H), 2.68 (d, 2H, J = 6.42 Hz), 3.75 (s, 6H), 5.31 (d, 1H, J= 3.78 Hz), 6.61 (d, 2H, J = 8.69 Hz), 7.06 (d, 1H, J = 3.40 Hz), 7.10 (s, 1H), 7.17 (t, 1H, J = 8.69, 8.31 Hz), APCI-MS *m/z* 515 $(M+H)^+$.

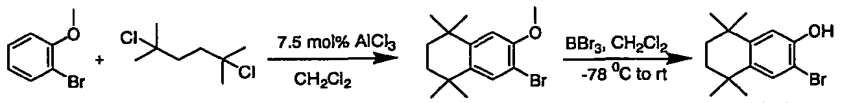
Example A8: 5-[(3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



A8

Compound A8 was synthesized according to Scheme A. The yield of the purified product was 25%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ1.22 (s, 6H), 1.28 (s, 6H), 1.66 (s, 4H), 3.80 (s, 9H), 5.41 (d, 1H), 6.15 (s, 2H), 7.06 (s, 1H), 7.18 (d, 1H), 7.51 (s, 1H), APCI-MS *m/z* 558.3 $(M+H)^+$.

The requisite phenol, 3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenol, was prepared as follows:



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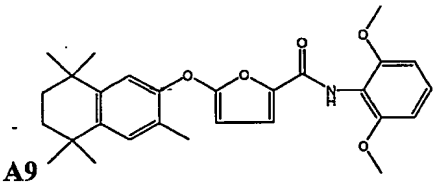
6-bromo-7-methoxy-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (i): A solution of 2-bromoanisole, 2,5-dichloro-2,5-dimethylhexane (1.1 equiv.) in dichloromethane (2 mL/mmol) was stirred at 0 °C under nitrogen as anhydrous $AlCl_3$ (7.5 mol%) was added portionwise while keeping the temperature below 5 °C. The suspension was allowed to warm to room temperature and further stirred for about 15

hours. The resulting white suspension was poured into ice water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The white solid thus obtained was recrystallized from toluene to give 6-bromo-7-methoxy-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene in 78% isolated yield. NMR data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.27 (s, 6H), 1.61 (s, 4H), 3.80 (s, 3H), 6.80 (s, 1H), 7.40 (s, 1H).

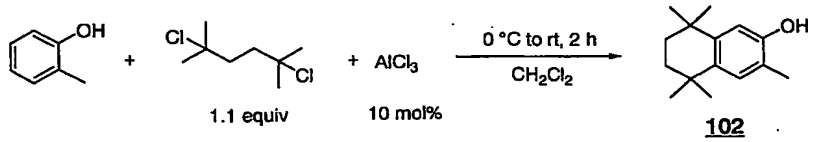
3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenol (ii): 6-Bromo-7-methoxy-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene in CH_2Cl_2 (3 mL/mmol) was demethylated by adding borontribromide (1.2 equiv.) in CH_2Cl_2 at –78 °C. The reaction mixture was allowed to warm to room temperature and further stirred for 15 hours. The solution was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to give 3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenol in 90% yield. NMR data consistent with the desired title product was as follows: ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 12H), 1.68 (s, 4H), 5.28 (s, 1H), 6.94 (s, 1H), 7.32 (s, 1H).

Example A9: N-(2,6-dimethoxyphenyl)-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy)-2-furamide



A9

Compound A9 was synthesized according to Scheme A via HATU. The yield for purified product was 27%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 6H), 1.28 (s, 6H), 1.67 (s, 4H), 3.85 (s, 3H), 5.34 (d, 1H), 6.62 (d, 2H), 7.01 (s, 1H), 7.13 (d, 1H), 7.15 (s, 1H), 7.23 (s, 1H), 7.26 (s, 1H), 7.34 (br s, 1H), APCI-MS m/z 464.1 $(M+H)^+$.



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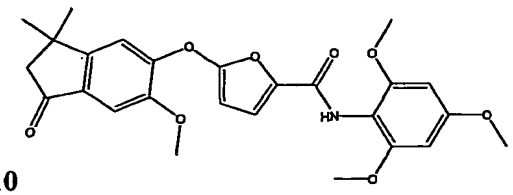
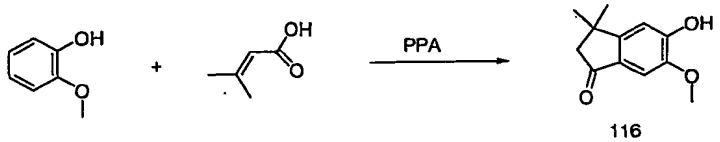
Example A10: 6-methoxy-3,3-dimethyl-1-oxo-N-(2,4,6-trimethoxypehnyl)-5-indanecarboxamide



A10

Compound A10 was synthesized in a manner analogous to that of A1, according to Scheme A, using similar starting compounds and reaction conditions. The overall yield is 5%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (s, 6H), 2.62 (s, 2H), 3.81 (s, 9H), 3.92 (s, 3H), 5.69 (d, 1H), 6.24 (s, 2H), 7.20 (s, 1H), 7.32 (s, 1H), APCI-MS *m/z* 482.1 $(M+H)^+$.



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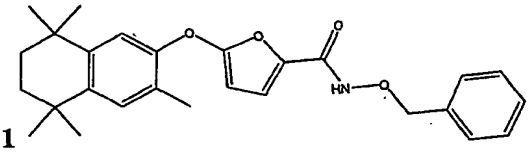
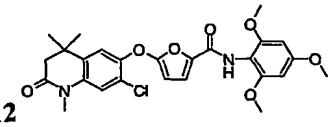
Example A11: N-(benzyloxy)-5-{(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy}-2-furamide



A11

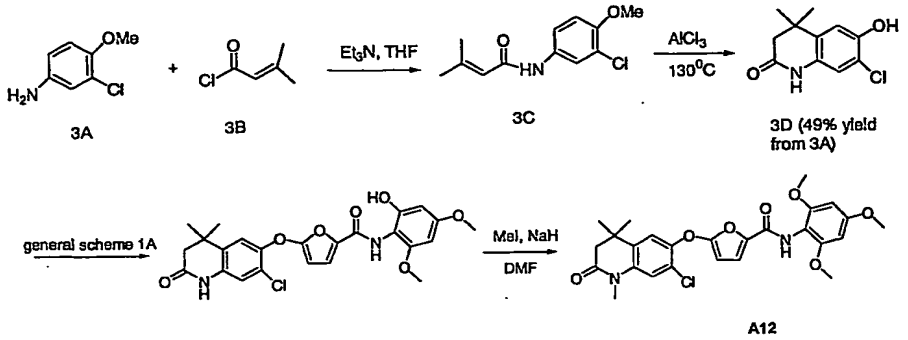
Compound A11 was synthesized in a manner analogous to that of A1, according to Scheme A, using similar starting compounds and reaction conditions. The overall yield was 33%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}HNMR(300 MHz, $CDCl_3$): δ 1.20 (s, 6H), 1.26 (s, 6H), 1.78 (s, 4H), 2.21 (s, 3H), 5.00 (s, 2H), 5.30 (d, 2H), 6.90 (s, 1H), 7.10 (s, 1H), 7.14 (d, 1H), 7.40 (m, 5H), 8.56 (br s, 1H), APCI-MS *m/z* 434.1 $(M+H)^+$.

Example A12: 5-[(7-chloro-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



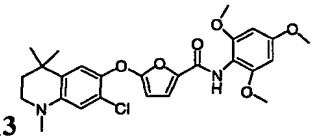
A12

Compound A12 was synthesized in a manner analogous to that of A1, according to the following scheme:



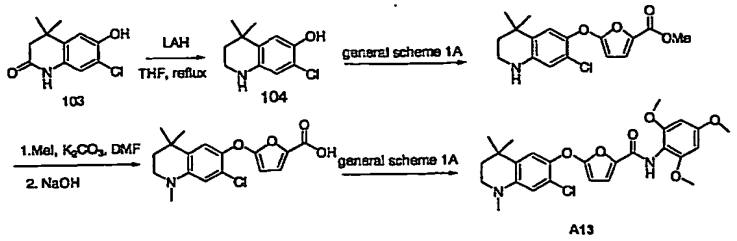
To a solution of Compound 3A (10g) and 3B (7.5g) in THF (200 ml) was added EtN_3 (6.5g). The solution was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc, dried and concentrated to give 16 g of 3C as brown oil...The residue was dissolved in 100 ml of CH_2Cl_2. To this solution was added $AlCl_3$ (33g). The solution was concentrated. The mixture was heated to 130°C in an oil bath under N_2 overnight. The mixture was cooled to room temperature and extracted with EtOAC. Compound 3D was precipitated in CH_3CN (7.3g). To a solution of Compound 3A (10g) and 3B (7.5g) in THF (200 ml) was added EtN_3 (6.5g). The solution was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc, dried and concentrated to give 16 g of 3C as brown oil...The residue was dissolved in 100 ml of CH_2Cl_2. To this solution was added $AlCl_3$ (33g). The solution was concentrated. The mixture was heated to 130°C in an oil bath under N_2 overnight. The mixture was cooled to room temperature and extracted with EtOAC. Compound 3D was precipitated in CH_3CN (7.3g). NMR and mass spectrometry data consistent with the desired title product were as follows: ^1H NMR (MeOD): δ 1.29 (s, 6H), 2.54 (s, 2H), 3.41 (s, 3H), 3.88 (s, 9H), 5.45 (d, 1H), 6.21 (s, 2H), 7.10 (s, 1H), 7.14 (d, 1H), 7.19 (s, 1H), APCI-MS *m/z* 515.2 $(M+H)^+$.

Example A13: 5-[(7-chloro-1,4,4-trimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



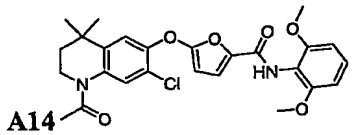
A13

Compound A13 was synthesized in a manner analogous to that of A1, according to the following scheme:

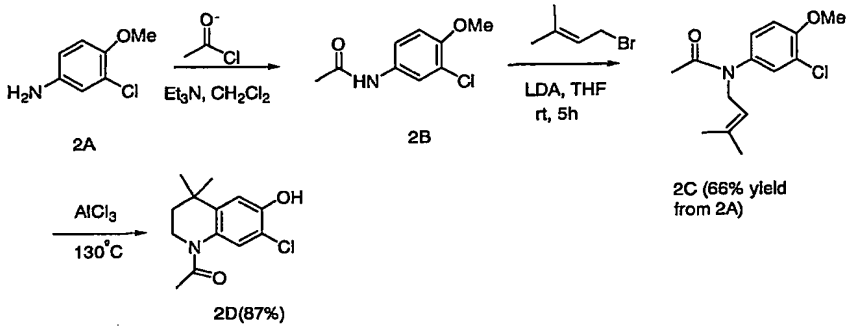


NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}HNMR (DMSO-d6): δ 1.20 (s, 6H), 1.69 (t, 2H), 3.22 (t, 2H), 3.71 (s, 6H), 3.78 (s, 3H), 5.29 (d, 1H), 6.26 (s, 2H), 6.63 (s, 1H), 7.21 (d, 1H), 8.9 (s, 1H), APCI-MS *m/z* 501.1 $(M+H)^+$.

Example A14: 5-[(1-acetyl-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,6-dimethoxyphenyl)-2-furamide



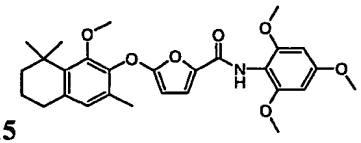
Compound A14 was synthesized in a manner analogous to that of A1, according to Scheme A, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}HNMR (DMSO-d6): δ 1.17 (s, 6H), 1.68 (t, 2H, J = 6.04 Hz), 2.15 (s, 3H), 3.64 (s, 2H), 3.65 (m, 6H), 5.54 (d, 1H, J = 3.40 Hz), 6.63 (d, 2H, J = 8.50 Hz), 7.17 (d, 2H, J = 16.81 Hz), 7.35 (s, 1H), 7.83 (s, 1H), 9.04 (s, 1H), APCI-MS *m/z* 499 $(M+H)^+$.



To a solution of 2A (11 g) and triethylamine (8.5 g) in CH_2Cl_2 was added acetylchlorode (6.6 g) slowly at room temperature. The solution was stirred for I hour, extracted with CH_2Cl_2 and concentrated to give compound 2B. Without purification the crude product was dissolved in THF (100 mL). To this solution was added LDA (1.3 eq.) followed by addition of allylbromide (11.3 g) at rt. The solution was stirred

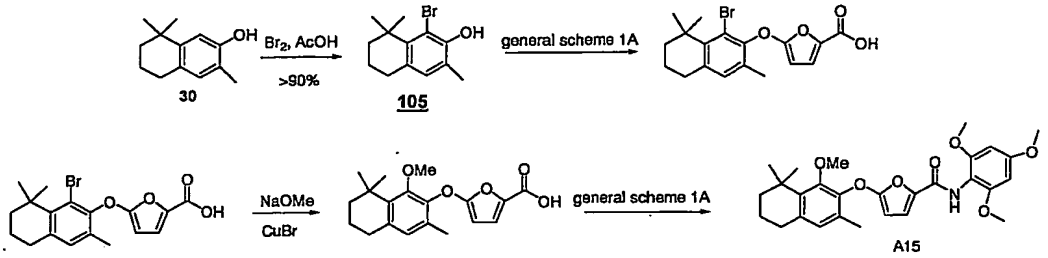
overnight. Compound 2C (12.4g) was isolated by column chromatography (hexane/EtoAC 2/1) Compound 2C (9g, 33.7 mmol) and $AlCl_3$ (9.1g, 67.4 mmol) was dissolved in 100 ml of CH_3NO_2. The solvent was evaporated and the dried mixture was heated to 135^{0}C for 1.5 hours. The mixture was cooled to room temperature, dissolved in CH_3NO_2, poured into ice slow water and extracted with EtOAc. Column chromatography (hexane: EtOAc: 2:1) gave 2D (7.8g) in 87% yield.

Example A15: 5-[(1-methoxy-3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



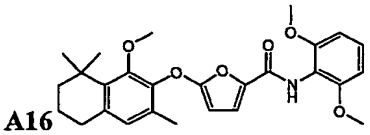
A15

Compound A15 was synthesized in a manner analogous to that of A1, according to Scheme A and the scheme set forth below:



NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (CH3OD): δ 1.37 (s, 6H), 1.64 (d, 2H, J = 10.20 Hz), 1.77 (d, 2H, J = 9.07 Hz), 2.17 (s, 3H), 2.71 (dd, 2H, J = 6.04, 5.67 Hz), 3.81 (s, 6H), 3.85 (s, 3H), 3.90 (s, 3H), 5.07 (d, 1H, J = 3.78 Hz), 6.26 (s, 2H), 6.75 (s, 1H), 7.11 (s, 1H), APCI-MS *m/z* 496 $(M+H)^+$.

Example A16: N-(2,6-dimethoxyphenyl)-5-[(1-methoxy-3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide

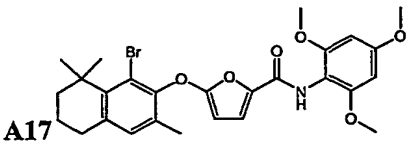


A16

Compound A16 was synthesized in a manner analogous to that of A15, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (CH3OD): δ 1.12 (s, 6H), 1.55 (d, 2H, J = 5.67 Hz), 1.72 (d, 2H, J = 4.15 Hz), 2.10 (s, 3H), 2.65

(dd, 2H, J = 6.42, 6.04 Hz), 3.63 (s, 3H), 3.73 (s, 6H), 5.32 (d, 1H, J = 3.78 Hz), 6.60 (m, 2H), 6.84 (s, 1H), 7.02 (s, 1H), 7.17 (t, 1H, J = 8.69, 8.31 Hz), APCI-MS *m/z* 466 $(M+H)^+$.

Example A17: 5-[(1-bromo-3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide

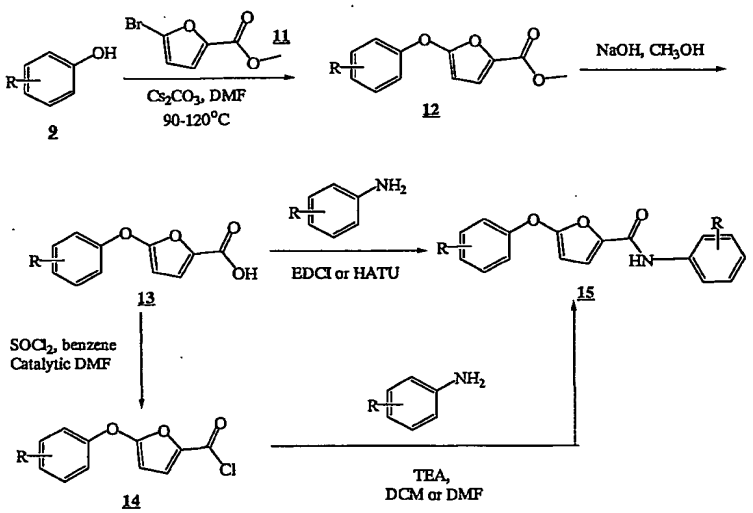


A17

Compound A17 was synthesized in a manner analogous to that of A15, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (CH3OD): δ 1.18 (s, 6H), 1.56 (m, 2H), 1.77 (m, 2H), 2.29 (s, 3H), 2.69 (t, 2H, J = 6.42 Hz), 3.70 (s, 6H), 3.75 (s, 3H), 5.32 (d, 1H, J = 3.78 Hz), 6.22 (s, 2H), 7.04 (d, 1H, J = 3.02 Hz), 7.10 (s, 1H), APCI-MS *m/z* 553 $(M+H)^+$.

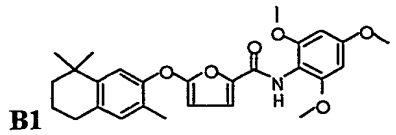
The following compounds were prepared according to Scheme B set forth below:

Scheme B



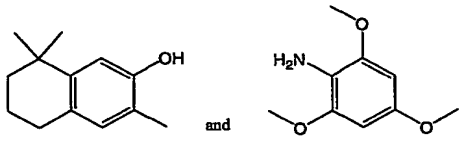
Scheme B is a modification of Scheme A. Numbered compounds and identified reagents of Scheme B are analogous to those similarly identified compounds and reagents of Scheme A.

Example B1: N-(2,4,6-trimethoxyphenyl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B1

Compound B1 was made according to Scheme B wherein:



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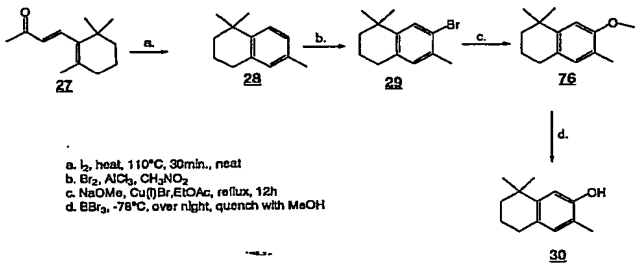
were used as the starting materials and the synthesis of the phenol is shown below. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}HNMR (300 MHz, CD_3OD): δ 7.38 (1H, d, J = 3.6 Hz), 7.32 (1H, s), 7.21 (1H, s), 6.52 (2H, s), 5.54 (1H, d, J = 3.6 Hz), 4.07 (3H, s), 4.05 (6H, s), 2.97 (2H, t, J = 6.23 Hz), 2.45 (3H, s), 2.10-1.89 (4H, m), 1.49 (6H, s), APCI-MS *m/z*: 466.2 $(M+H)^+$.

The requisite phenol was synthesized according to the procedure shown and described below:

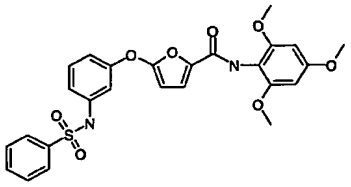


7-bromo-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene 29: 1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene was synthesized from beta-ionone as discussed in Parlow, TETRAB; *Tetrahedron*, EN, 49; 13; 2577-2588 (1993). To a solution containing 1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene 28 (1.0 eq, 7.5 g, 43.1 mmol, 0.2 M) in nitromethane, bromine (1.0 eq, 2.21 mL, 43.1 mmol) was added dropwise over 2 minutes. The solution was then stirred vigorously and aluminum trichloride (0.07 eq, 375 mgs, 2.81 mmol) was added solid. The mixture was stirred overnight and quenched with sodium thiosulfate and extracted with methylene chloride. The organic solvent was evaporated *in vacuo* and the crude mixture was dissolved in minimal amount of hexanes. The resulting liquid was loaded onto a silicagel (700 mL) plug column and eluted with hexanes to yield 50% 7-bromo-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene 29 (5.50 g).

7-methoxy-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene 76: To a flask containing 7-bromo-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene (1.0 eq, 60 g, 228 mmol), sodium methoxide (521 mL) was added along with ethyl acetate (80 mL) and Cu(I)Br (0.03 eq, 1g, 7.0 mmol). The solution was refluxed 24 hours and quenched with concentrated HCl. The solution was diluted with water and extracted with ethyl acetate. The crude was purified by silica gel using ethyl acetate hexane elution to yield 7-methoxy-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene 76 (19.88 g, 97 mmol, 43% yield).

3,8,8–trimethyl-5,6,7,8–tetrahydro-2–naphthalenol 30: 7-methoxy-1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene (1.0 eq, 5.67 g, 27.8 mmol) was dissolved in methylene chloride (0.2 M) and cooled to –78°C. To this solution, BBr_3 (1.0 eq, 1 M, 27 mL) was added at once and stirred overnight slowly bringing the solution to room temperature. The solution was then quenched with methanol and passed through a silicagel plug to yield 3,8,8–trimethyl-5,6,7,8–tetrahydro-2–naphthalenol 30 (4.68 g, 88%).

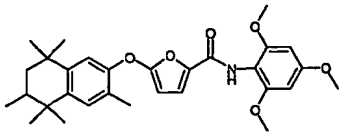
Example B2: 5-(3-Benzenesulfonylamino-phenoxy)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



B2

Compound B2 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

Example B3: 5-{[(6s)-3,5,5,6,88-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl]oxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide

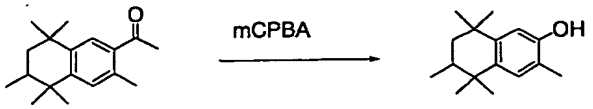


B3

Compound B3 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. Yield of purified product was 89%. NMR data consistent with the desired title product were as follows: ^1H (300 MHz, $CDCl_3$): δ 0.94 (d, 3H, J = 6.42 Hz), 1.08,

1.22, 1.25, 1.30 (4s, 3H each), 1.30 - 1.37 (m, 1H), 1.63 (t, J = 12.8 Hz), 1.78-1.93 (m, 1H), 2.23 (s, 3H), 4.6 (s, 1H, OH), 6.75 and 7.15 (2s, 1H each).

The requisite phenol was prepared by the following scheme:



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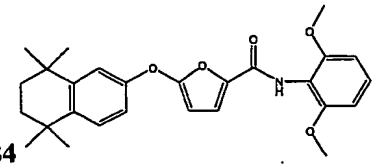
3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenol: To the solution of fixolide (25.84 g, 100 mmol) in dichloromethane (500 mL) was added m-chloroperbenzoic acid (57-86 % taken mean value of 71%, 12.08 g, 100 mmol). The resulting mixture was stirred for 16 hours at room temperature. The solvent was evaporated, and the residue was dissolved in methanol (200 mL). Sodium methoxide (457 mL of 25%, 200 mmol) was added. The mixture was stirred for 2 hours, and methanol evaporated. The residue was diluted with water and neutralized with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was filtered through a plug of silica gel. The solvent was evaporated and the residue on crystallization with ethyl acetate-hexane mixture gave white powder, 20.9 g.

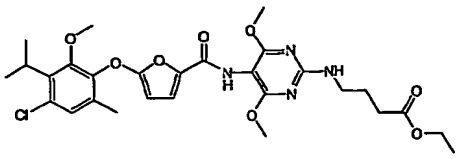
Example B4: N-(2,6-dimethoxyphenyl)-5-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B4

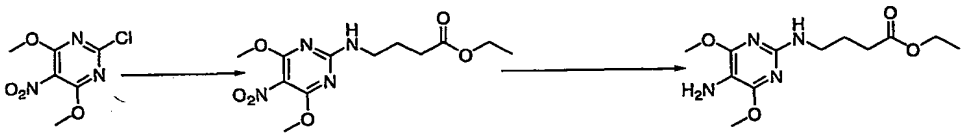
Compound B4 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 12H), 1.68 (s, 4H), 3.83 (s, 6H), 5.53 (d, 1H), 6.60 (d, 2H), 6.90 (d, 1H), 7.15 (s, 1H), 7.19 (d, 1H), 7.22 (t, 1H), 7.28 (d, 1H), APCI-MS m/z 450.3 $(M+H)^+$.

Example B5: ethyl 4-[(5-{[5-(4-chloro-3-isopropyl-2-methoxy-6-methylphenoxy)-2-furoyl]amino}-4,6-dimethoxy-2-pyrimidinyl)amino]butanoate



B5

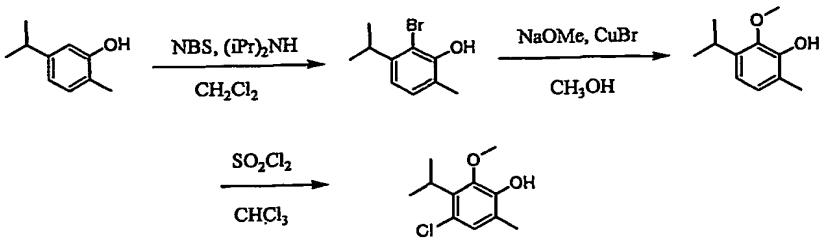
Compound B5 was synthesized by coupling of the pyrimidine derivative, the preparation of which is described below, to a substituted furoic acid according to Scheme B. NMR and mass spectrometry data consistent with the desired title product were as follows: 1HNMR ($CDCl_3$): δ 1.26 (3H, t), 1.40 (6H, d), 1.98 (2H, sextet), 2.19 (3H, s), 2.39 (2H, t), 3.48 (2H, q), 3.58 (1H, heptet), 3.83 (3H, s), 3.89 (6H, s), 4.12 (2H, q), 5.08 (1H, br t); 5.11(1H, d), 6.91 (1H, s), 7.03 (1H, s), 7.08 (1H, d), FI-PCI m/z 592.2 & 593.2 $(M+H)^+$.



II 117 118

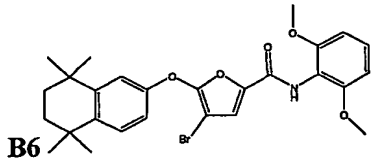
Displacement of 4-chloride: To a solution of 4-chloro-2,4-dimethoxy nitropyrimidine (3.28 g, 15 mmol) in DMF (30 mL) was added triethylamine (2.09 mL, 15 mol) and ethyl 4-aminobutyrate hydrochloride (2.51 g, 15 mmol). The reaction mixture was stirred at room temperature overnight. Most of DMF was removed on a rotovap. The concentrate was redissolved in ethyl acetate, washed with water, brine, dried over magnesium sulfate. The solvent was removed on a rotovap. The product was purified by flash chromatography (solvent: 1 ethyl acetate: 3 hexanes to 1 ethyl acetate: 2 hexanes): 2.38 g (50.5%). NMR data consistent with the desired title product were as follows: ^1H NMR ($CDCl_3$): δ 1.27 (3H, t), 1.98 (2H, sextet), 2.41 (2H, t), 3.49 (2H, q), 3.94 (3H, s), 4.01 (3H, s), 4.15 (2H, q), 5.50 (1H, br t).

Hydrogenation: The nitro pyrimidine compound obtained from above (2.38 g, 7.58 mmol) was dissolved in methanol (25 mL). 10% palladium on carbon catalyst (.4 g) was carefully added to the methanolic solution and the mixture was hydrogenated at 45-50 psi overnight. The mixture was then filtered through Celite and then washed with methanol. The combined filtrate was concentrated to a dark oil, 1.76 g (82%).



NMR and Mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, t), 1.98 (2H, sextet), 2.39 (2H, t), 2.49 (2H, br s), 3.48 (2H, q), 3.90 (6H, s), 4.12 (2H, q), 4.60 (1H, br t), FI-PCI m/z 285.2 $(M+H)^+$.

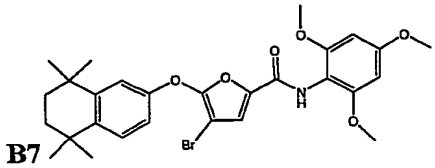
Example B6: 4-bromo-5-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B6

Compound B6 was synthesized in a manner analogous to that of B1, according to Scheme B. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, CD_3OD): δ 1.52 (s, 12H), 1,96 (s, 4H), 4.06 (s, 6H), 6.94 (d, 2H), 7.09 (d, 1H), 7.28 (s, 1H), 7.54 (t, 2H), 7.62 (d, 1H), APCI-MS m/z 528.3 $(M+H)^+$.

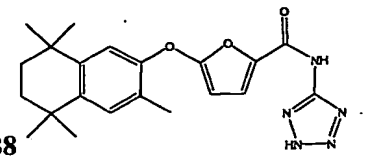
Example B7: 4-bromo-5-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B7

Compound B7 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, CD_3OD): δ 1.26 (s, 12H), 1,70 (s, 4H), 3.77 (s, 3H), 3.80 (s, 6H), 6.25 (s, 2H), 6.81 (d, 1H), 7.01 (s, 1H), 7.27 (s, 1H), 7.32 (d, 1H), APCI-MS m/z 558.4 $(M+H)^+$.

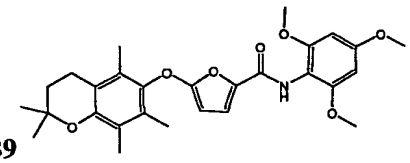
Example B8: 5-[(3,5,5,8',8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2H-tetrazol-5-yl)-2-furamide



B8

Compound B8 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (CD_3OD-d4): δ 1.25 (s, 6H), 1.30 (s, 6H), 1.72 (s, 4H), 2.23 (s, 3H), 5.41(d, 1H), 7.08 (s, 1H), 7.28 (s, 1H), 7.45 (d, 1H), LC-MS, APCI, $(M+H)^+$: 396.

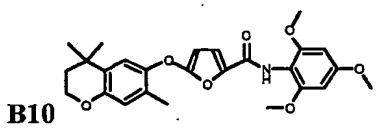
Example B9: 5-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2h-chromen-6-yl)oxy]-n-(2,4,6-trimethoxyphenyl)-2-furamide



B9

Compound B9 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.81 (t, 2H), 2.05 (s, 3H), 2.11 (s, 6H), 2.62 (t, 2H), 3.81 (s, 9H), 4.91 (d, 1H), 6.19 (s, 2H), 7.08 (d, 1H), 7.22 (s, 1H), APCI-MS *m/z* 496.1 $(M+H)^+$.

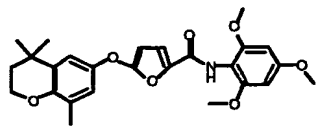
Example B10: N-(2,4,6-trimethoxyphenyl)-5-[(4,4,7-trimethyl-3,4-dihydro-2h-chromen-6-yl)oxy]-2-furamide



B10

Compound B10 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 26%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.84 (dd, 2H, J = 4.14, 6.23 Hz), 2.21 (s, 3H), 3.81 (br s, H_2O), 3.81 (s, 9H), 4.2 (dd, 2H, J = 4.23, 6.23 Hz), 5.22 (d, 1H, J = 3.4 Hz), 6.19 (s, 2H), 6.69 (s, 1H), 7.03 (s, 1H), 7.17 (d, 1H, J = 3.02 Hz), 7.31 (br s, 1H), APCI-MS *m/z* 468.2 $(M+H)^+$.

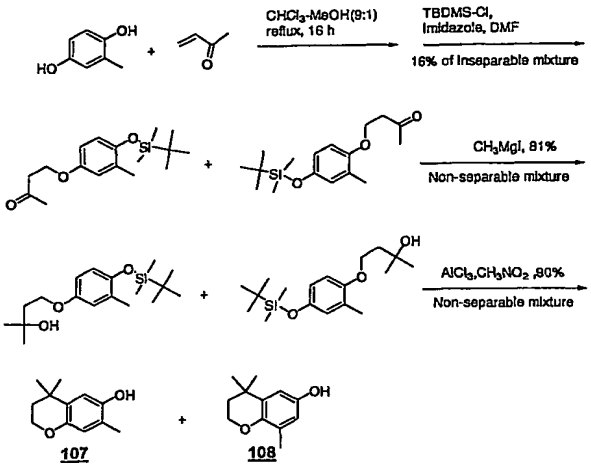
Example B11: N-(2,4,6-trimethoxyphenyl)-5-[(4,4,8-trimethyl-3,4-dihydro-2h-chromen-6-yl)oxy]-2-furamide



B11

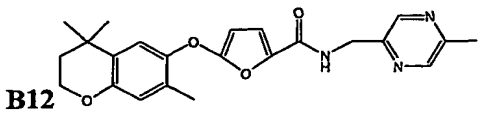
Compound B11 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 26%.

The requisite chromanophenol was synthesized according to the following method:



The mixture of these chromanophenols was treated with methyl bromofuroate. The final products were separated using HPLC. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 6H), 1.75 (t, 2H, J = 5.29 Hz), 2.10 (s, 3H), 3.73 (s, 9H), 4.13 (t, 2H, J = 5.29 Hz), 4.25 (br s, H_2O), 5.32 (d, 1H, J = 3.59 Hz), 6.08 (s, 2H), 6.69 (d, 1H, J = 3.03 Hz), 6.84 (d, 1H, J = 3.03 Hz), 7.10 (d, 1H, J = 3.59 Hz), 7.31 (br s, 1H), APCI-MS *m/z* 468.2 $(M+H)^+$.

Example B12: N-[(5-methyl-2-pyrazinyl)methyl]-5-[(4,4,7-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide

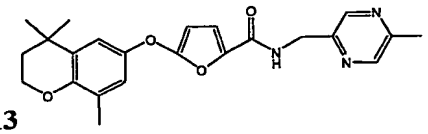


B12

Compound B12 was synthesized in a manner analogous to that of B11, according to Scheme B, using similar starting compounds and reaction conditions.

The yield of the purified product was 12%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 6H), 1.83 (t, 2H, J = 5.48 Hz), 2.18, 2.62 (2s, 3H each), 4.19 (t, 2H, J = 5.48 Hz), 5.06 (br s, H_2O), 5.19 (d, 1H, J = 3.58 Hz), 6.68 (s, 1H), 6.99 (s, 1H), 7.11 (d, 1H, J = 3.58 Hz), 7.13 (br s, 1H), 8.48, 8.60 (2s, 1H each), APCI-MS *m/z* 408.1 $(M+H)^+$.

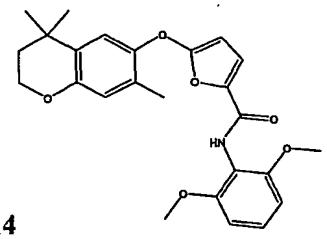
Example B13: N-[(5-methyl-2-pyrazinyl)methyl]-5-[(4,4,8-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B13

Compound B13 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 11%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.85 (dd, 2H, J = 5.29, 5.47 Hz), 2.18, 2.63 (2s, 3H each), 4.23 (dd, 2H, J = 5.29, 5.48 Hz), 4.78 (d, 2H, J = 5.47 Hz), 5.39 (d, 1H, J = 3.59 Hz), 6.14 (br s, H_2O), 6.66 (d, 1H, J = 2.83 Hz), 6.92 (d, 1H, J = 3.02 Hz), 7.13 (d, 1H, J = 3.58 Hz), 7.17 (br s, 1H), 8.50, 8.62 (2s, 1H each), APCI-MS *m/z* 408.1 $(M+H)^+$.

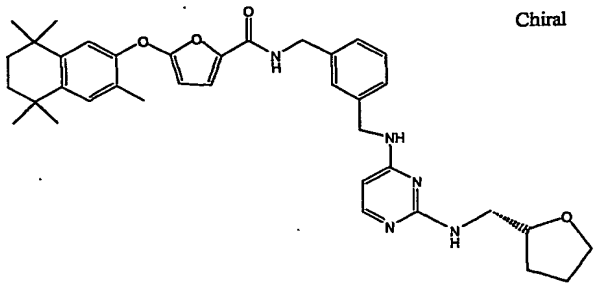
Example B14: N-(2,6-dimethoxyphenyl)-5-[(4,4,7-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B14

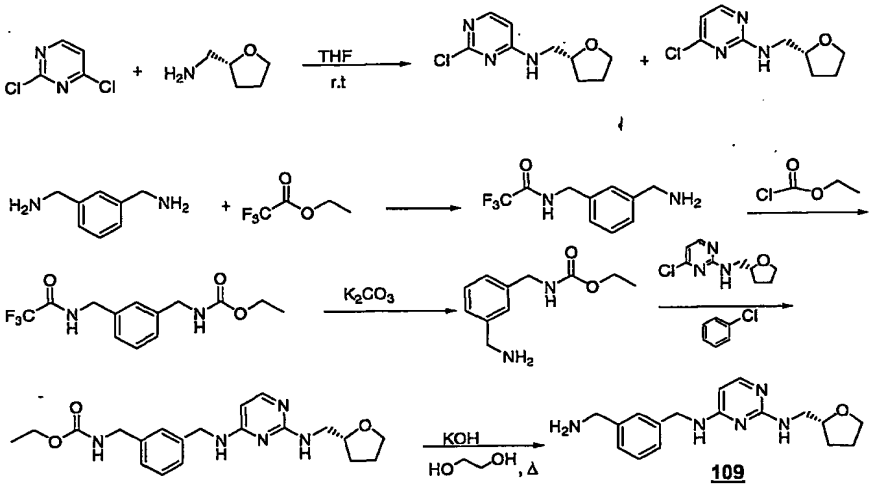
Compound B14 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 66%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 6H), 1.81 (t, 2H, J = 5.48 Hz), 2.19 (s, 3H), 3.84 (s, 6H), 4.17 (t, 2H, J = 5.29 Hz), 5.21 (d, 1H, J = 3.59 Hz), 6.62 (m, 2H), 7.01 (s, 1H), 7.15 (d, 1H, J = 3.4 Hz), 7.21 (t, 1H, J = 8.5 Hz), 7.40 (br s, 1H), MS m/z 438.2 $(M+H)^+$.

Example B15: 5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(3-{[(2-{[(2R)tetrahydro-2-furanylmethyl]amino}-4-pyrimidinyl)amino]methyl}benzyl)-2-furamide



B15

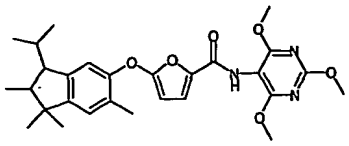
Compound B15 was synthesized according to Scheme B.



Preparation of 2-chloro-N-[(2R)-tetrahydro-2-furanmethyl]-4-pyrimidinamine & 4-chloro-N-[(2R)-tetrahydro-2-furanmethyl]-2-pyrimidinamine: To a 250 mL round bottom flask was placed 2,4-dichloropyrimidine (5.0g, 33.56 mmol) and 200 mL THF. To this solution was added triethylamine (14.0 mL, 100.68 mmol) and [R]-tetrahydrofurfurylamine. The solution was stirred overnight. The reaction mixture was poured into water and extracted with methylene chloride. The separated organic layer was washed with brine, dried over magnesium sulfate, and concentrated on a rotary evaporator. The crude compound was purified by silica gel chromatography with hexane/ ethyl acetate (4:1 v/v to 1:1 v/v) to yield chloro-N-[(2R)-tetrahydro-2-furanmethyl]-2-pyrimidinamine (1.3 g) and 2-chloro-N-[(2R)-tetrahydro-2-furanmethyl]-4-pyrimidinamine (3.98 g). Preparation of N-[3-(aminomethyl)benzyl]-2,2,2-trifluoroacetamide: To a solution of m-xylene diamine (28.76g, 211.15 mmol) in THF (300 mL, .7M) was added dropwise a solution of ethyl trifluoroacetate (10g, 70.38 mmol) in THF (50 mL, 1.4M). The solution was stirred at room temperature

overnight. The reaction was monitored by TLC. The solvent was concentrated and residue was acidified to pH 2 with 4N HCl and dissolved in water and washed with ethyl acetate. The separated aqueous layer was basified to pH 11 using NH_4OH and compound was extracted with dichloromethane. The separated organic layer was wash with water/brine, dried over magnesium sulfate and concentrated to yield N-[3-(aminomethyl)benzyl]-2,2,2-trifluoroacetamide (8.71g, 53% yield). Preparation of ethyl 3-(aminomethyl)benzylcarbamate: To a solution of N-[3-(aminomethyl)benzyl]-2,2,2-trifluoroacetamide (10.6g, 43.1 mmol) was added ethyl chloroformate (1eq.) followed by triethylamine.. Reaction was stirred at room temperature for 30 min. Crude product was extracted with methylene chloride and concentrated to give ethyl 3-{[(trifluoroacetyl)amino]methyl} benzylcarbamate 4. This crude product was dissolved in methanol (100 mL) and 2N K_2CO_3 (100 mL) and stirred overnight. Reaction mixture was basified to pH 14 with 20% NaOH, extracted with methylene chloride, wash with brine and dried over magnesium sulfate to yield ethyl 3-(aminomethyl)benzylcarbamate (5.2g).Preparation of ethyl 3-{[(2-{[(2R)-tetrahydro-2furanylmethyl]amino}-4-pyrimidinyl)amino]methyl}benzylcarbamate: To a solution of ethyl 3-(aminomethyl)benzylcarbamate and 4-chloro-N-[(2R)-tetrahydro-2-furanmethyl]-2-pyrimidinamine in chlorobenzene was added triethylamine. Reaction mixture was reflux overnight. The solution was cooled to room temperature and loaded on a silica gel column and eluted with hexane/ethyl acetate (1:1 v/v) to yield ethyl 3-{[(2-{[(2R)-tetrahydro-2-furanylmethyl]amino}-4-pyrimidinayl)amino]methyl}benzylcarbamate (73% yield). Ethyl 3-{[(2-{[(2R)-tetrahydro-2-furanylmethyl]amino}-4-pyrimidinayl) amino]methyl}benzylcarbamate was dissolved in ethylene glycol and potassium hydroxide (1:1 v/v). The solution was heated to 100°C overnight. The mixture was cooled to room temperature and extracted with chloroform, washed with brine, and dried over magnesium sulfate to yield N^4-[3-(aminomethyl0benzyl]-N^2-[(2R)-tetrahydro-2-furanylmethyl]-2,4-pyrimidinediamine (82 % yield). NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}HNMR (CDCl3): δ 1.20 (s, 6H), 1.25 (s, 6H), 1.66 (s, 4H), 1.87-1.99 (m, 4H), 2.21 (s, 3H), 3.74-3.89 (m, 2H), 3.75 (t, 1H), 3.87 (t, 1H), 3.88 (m, 1H), 4.5 (d, 2H), 4.58 (d, 2H), 5.30 (d, 1H), 5.73 (d, 1H), 6.57 (t, 1H), 6.94 (s, 1H), 7.08 (d, 1H), 7.14 (s, 1H), 7.23-7.34 (m, 5H) (s, 1H), 7.76 (d, 1H), APCI-MS *m/z* 624.4 $(M+H)^+$.

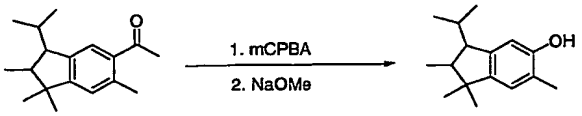
Example B16: 5-[(3-isopropyl-1,1,2,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B16

Compound B16 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds where the nitro-pyrimidine is compound VII which was reduced to the amine in a manner analogous to that of compund III and the synthesis of the phenol is shown below. The yield of the purified product was 61%.

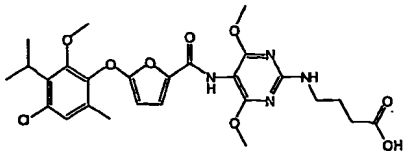
The requisite phenol, 3-isopropyl-1,1,2,6-tetramethyl-5-indanol, was synthesized according to the following method:



110

To the solution of transeolide (5.16 g, 20 mmol) in dichloromethane (100 mL) was added m-chloroperbenzoic acid (57-86% taken mean value of 71%, 5.83 g, 24 mmol) and sodium bicarbonate (1.7 g, 20 mmol). The reaction mixture was stirred for 16 hours at room temperature. The solvent evaporated, the residue was dissolved in methanol (100 mL). Sodium methaoxide (13.72 mL of 25% methanolic soution, 60 mmol) was added and the mixture was stirred at room temperature for 2 hours, and solvent evaporated. The residue was diluted with water (150 mL), neutralized with diluted hydrochloric acid, and extracted with ethyl acetate (500 mL). The organic layer was dried and filtered through a small plug of silica gel to give desired phenol as white solid (4.29 g, 92%). NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 0.96 (d, 6H, J = 9.8 Hz), 1.01 (s, 3H), 1.09 (d, 3H, J = 9.0 Hz), 1.27 (s, 3H), 1.8-1.95 and 2.1-2.25 (2m, 1H each), 2.25 (s, 3H), 2.73 (d, 1H, J = 9.82 Hz), 3.95 (s, 6H), 3.98 (s, 3H), 5.32 (d, 1H, J = 3.58 Hz), 6.91 (s, 1H), 7.05 (s, 1H), 7.15 (d, 1H, J = 3.59 Hz), APCI-MS *m/z* 510.3 $(M+H)^+$.

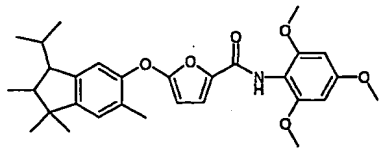
Example B17:4-[(5-{[5-(4-chloro-3-isopropyl-2-methoxy-6-methylphenoxy)-2-furoyl]amino}-4,6-dimethoxy-2-pyrimidinyl)amino]butanoic acid



B17

Compound B17 was synthesized from Compound B5. Compound B5 (53 mg, 0.089 mmol) was dissolved in ethanol (1 mL) and an aqueous solution of sodium hydroxide (2 equivalents) was added. The reaction was monitored by TLC (developing solvent: 5% methanol in methylene chloride) for completion of reaction. After saponification was complete, the mixture was concentrated. The residue was diluted with water and washed with ether. The aqueous layer was then carefully acidified to pH 2 with 10% HCl and the product was extracted with methylene chloride. The title product was purified by silica gel chromatography (solvent: 10% methanol in methylene chloride). NMR and Mass spectrometry data consistent with the desired title product were as follows: ^{1}H NMR ($CDCl_3$):, δ 1.35 (6H, d), 1.95 (2H, sextet), 2.19 (3H, s), 2.43 (2H, t), 3.47 (2H, q), 3.58 (1H, heptet), 3.83 (3H, s), 3.89 (6H, s), 5.11(1H, d), 5.30 (1H, br t); 6.93 (1H, s), 7.01 (1H, s), 7.08 (1H, d); FI-PCI m/z 564.2 & 565.2 $(M+H)^+$.

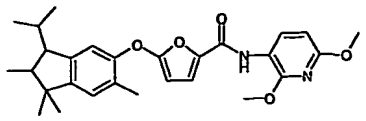
Example B18: 5-[(3-isopropyl-1,1,2,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B18

Compound B18 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 55%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, CH_3OH-d_4): δ 0.96 (d, 6H, J = 8.87 Hz), 0.99 (s, 3H), 1.01 (d, 3H, J = 6.98 Hz), 1.28 (s, 3H), 1.70-1.95 and 2.1-2.25 (2m, 1H each), 2.26 (s, 3H), 2.71 (d, 1H, J = 9.25 Hz), 3.80 (2s, 3H each), 3.82 (s, 3H), 5.31 (d, 1H, J = 3.58 Hz), 6.27 (2s, 1H each), 6.92 and 7.06 (2s, 1H each), 7.15 (br s, 1H), APCI-MS *m/z* 508.2 $(M+H)^+$.

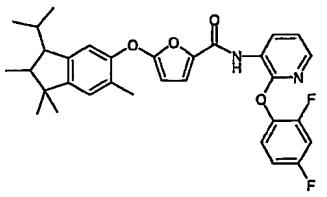
Example B19: N-(2,6-dimethoxy-3-pyridinyl)-5-[(3-isopropyl-1,1,2,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B19

Compound B19 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 28 %. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, CH_3OH-d_4): δ 0.95 (d, 6H, J = 7.18 Hz), 1.00 (s, 3H), 1.09 (d, 3H, J = 6.98 Hz), 1.27 (s, 3H), 1.80-1.95 and 2.1 - 2.25 (2m, 1H each), 2.25 (s, 3H), 2.71 (d, 1H, J = 8.31 Hz), 3.90 and 4.0 (2s, 3H each), 5.33 (d, 1H, J = 3.58 Hz), 6.33 (d, 1H, J = 8.31 Hz), 6.92 and 7.06 (2s, 1H each), 7.16 (d, 1H, J = 3.78 Hz), 8.05 (d, 1H, J = 8.5 Hz), APCI-MS *m/z* 479.2 $(M+H)^+$.

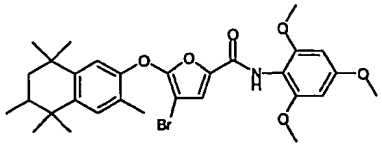
Example B20: N-[2-(2,4-difluorophenoxy)-3-pyridinyl]-5-[(3-isopropyl-1,1,2,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B20

Compound B20 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 32 %. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, CH_3OH-d_4): δ 0.91 (d, 6H, J = 6.99 Hz), 1.00 (s, 3H), 1.04 (d, 3H, J = 6.80 Hz), 1.24 (s, 3H), 1.80-1.95 and 2.1-2.25 (2m, 1H each), 2.22 (s, 3H), 2.65 (d, 1H, J = 9.07 Hz), 5.36 (d, 1H, J = 3.78 Hz), 6.91 (s, 1H), 6.95-7.15 (m, 4H), 7.26 (d, 1H, J = 3.78 Hz), 7.26-7.37 (m, 1H), 7.80 (dd, 1H, J = 6.6, 1.7 Hz), 8.47 (dd, 1H, J = 9.44 and 1.70 Hz), APCI-MS *m/z* 547.2 $(M+H)^+$.

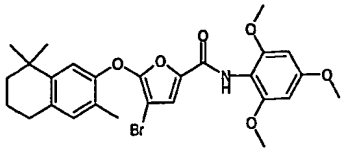
Example B21: 4-bromo-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B21

Compound B21 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 16 %. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 0.97 (d, 3H, J = 6.61 Hz), 1.05, 1.20, 1.22, 1.31 (4s, 3H each), 1.30-1.45 (m, 1H), 1.50-1.70 (m, 1H), 1.80-2.0 (m, 1H), 2.33 (s, 3H), 3.79 (2s, 6H), 3.81 (s, 3H), 5.34 (d, 1H, J = 3.4 Hz), 6.15 (s, 2H), 6.79 (s, 1H), 7.08 (br s, 1H), 7.18 and 7.19 (2s, 1H each), APCI-MS *m/z* 586.2 and 588.2 $(M+H)^+$.

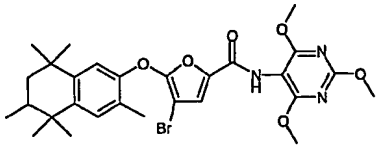
Example B22: 4-bromo-N-(2,4,6-trimethoxyphenyl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B22

Compound B22 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 18%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.55 - 1.66 (m, 2H), 1.73 - 1.83 (m, 2H), 2.29 (s, 3H), 2.70 (t, 1H, J = 6.24 Hz), 3.78 (s, 6H), 3.81 (s, 3H), 6.16 (s, 2H), 6.85,6.90, 7.07 (br) and 7.19 (4s, 1H each), APCI-MS *m/z* 544.2 and 545.2 $(M+H)^+$.

Example B23: 4-bromo-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide

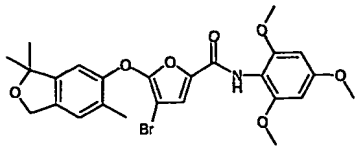


B23

Compound B23 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 8%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 0.98 (d, 3H, J = 6.61 Hz), 1.05, 1.20, 1.21, 1.32 (4s, 3H each), 1.30-1.45 (m, 1H), 1.61 (dd, 1H, J = 12.8, 13.2 Hz), 1.77 - 1.92 (m, 1H), 2.32 (s, 3H), 3.94 (s, 6H), 3.94 (s,

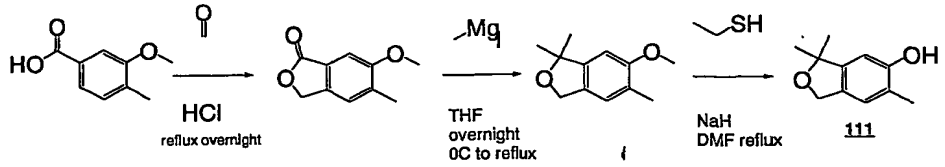
3H), 6.77 (s, 1H), 6.93 (br s, 1H), 7.19 and 7.22 (2s, 1H each), APCI-MS *m/z* 588.2 and 590.2 $(M+H)^+$.

Example B24: 4-bromo-N-(2,4,6-trimethoxyphenyl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]2-furamide



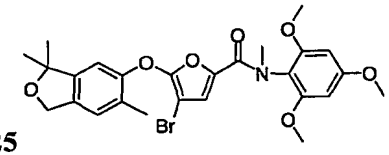
B24

Compound B24 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 21%.



NMR and mass spectrometry data consistent with the desired title product were as follows: ^1H (300 MHz, $CDCl_3$): δ 1.46 and 2.37 (2s, 6H and 3H respectively), 3.81 (s, 6H), 3.99 (s, 3H), 5.01, 6.16 (2s, 2H each), 6.62 and 7.05 (2s, 1H each), 7.09 (brs, 1H), 7.20 (s, 1H), APCI-MS *m/z* 533 and 534 $(M+H)^+$.

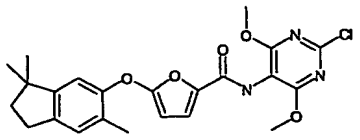
Example B25: 4-bromo-N-methyl-N-(2,4,6-trimethoxyphenyl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B25

Compound B25 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 20%. NMR and mass spectrometry data consistent with the desired title product were as follows: ^1H (300 MHz, $CDCl_3$): δ 1.41 (s, 6H), 2.24 and 3.17 (2s, 3H each), 3.70 (s, 6H), 3.82 (s, 3H), 4.98, 6.04 (2s, 2H each), 6.08 (s, 2H), 6.50 and 6.97 (2s, 1H each), APCI-MS *m/z* 533 and 546 and 548 $(M+H)^+$.

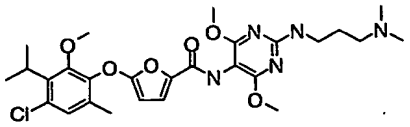
Example B26: 5-(3,3,6-Trimethyl-indan-5-yloxy)-furan-2-carboxylic acid (2-chloro-4,6-dimethoxy-pyrimidin-5-yl)-amide



B26

Compound B26 was synthesized in a manner analogousto that of B1, according to scheme B.

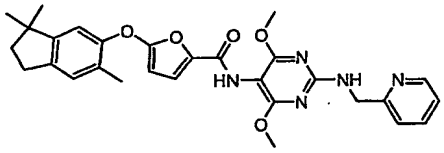
Example B27: 5-(4-chloro-3-isopropyl-2-methoxy-6-methylphenoxy)-N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxy-5-pyrimidinyl)-2-furamide



B27

Compound B27 was synthesized in a manner analogousto that of B1, according to scheme B.

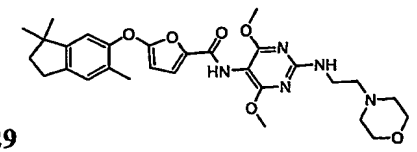
Example B28: N-{4,6-dimethoxy-2-[(pyridin-2-ylmethyl)amino]pyrimidin-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B28

Compound B28 was synthesized in manner analogous to that of B52. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.93(dd, 2H, J = 14.35, 7.18, Hz), 2.24 (s, 3H), 2.84 (t, 2H, J = 14.35 Hz), 3.86 (s, 6H), 4.72 (d, 2H, J = 6.04 Hz), 5.28 (s, 1H), 5.84 (dd, 1H, J = 11.33, 5.67 Hz), 6.82 (s, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.09 (d, 1H, J = 3.78 Hz), 7.18 (d, 1H, J = 11.71 Hz), 7.35 (d, 1H, J = 7.93 Hz), 7.66 (dd, 1H, J = 15.49, 7.93 Hz), 8.56 (d, 1H, J = 4.91 Hz), APCI-MS m/z 530.6 $(M+H)^+$.

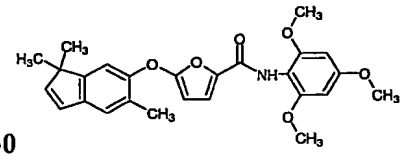
Example B29: N-{4,6-dimethoxy-2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B29

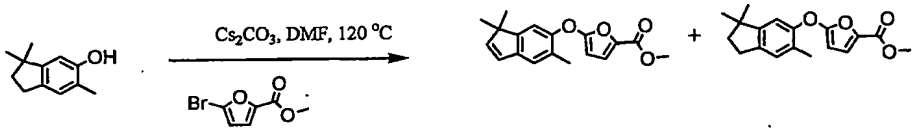
Compound B29 was synthesized in manner analogous to that of B52. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.93 (dd, 2H, J =1 4.35, 7.18 Hz), 2.24 (s, 3H), 2.50 (s, 4H), 2.59 (t, 2H, J = 12.09 Hz), 2.84 (dd, 2H, J = 14.35, 7.18 Hz), 3.49 (dd, 1H, J = 11.71, 5.67 Hz), 3.75 (tt, 4H, J = 9.07, 4.53 Hz), 3.88 (s, 6H), 5.27(d, 1H, J = 3.78 Hz), 5.36 (d, 1H, J = 10.20 Hz), 6.82 (s, 1H), 6.95 (s, 1H), 7.05 (s, 1H), 7.10 (d, 1H, J=3.40 Hz), APCI-MS m/z 552.6 $(M+H)^+$.

Example B30: *N*-(2,4,6-trimethoxyphenyl)-5-[(1,1,5-trimethyl-*1H*-inden-6-yl)oxy]-2-furamide



B30

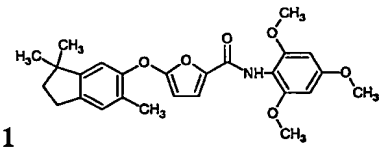
Compound B30 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



Note: the reaction content were not degassed before heating

NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 8.89 (bs, 1H), 7.24 (s, 2H), 7.18 (bd, 1H, J = 3 Hz), 6.63 (d, 1H, J = 6 Hz), 6.45 (d, 1H, J = 6 Hz), 6.26 (s, 2H), 5.47 (d, 1H, J = 3 Hz), 3.79 (s, 3H), 3.71 (s, 6H), 2.24 (s, 3H), 1.23 (s, 6H).

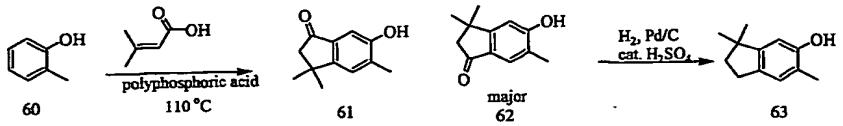
Example B31: *N*-(2,4,6-trimethoxyphenyl)-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B31

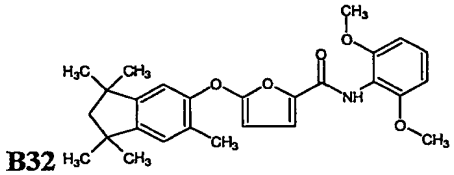
Compound B31 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

The requisite phenol was synthesized according to the following method:



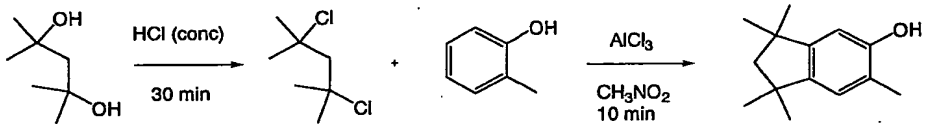
NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.17 (bs, 1H), 7.10 (d, 1H, J = 3 Hz), 7.05 (s, 1H), 6.84 (s, 1H), 6.17 (s, 2H), 5.29 (d, 1H, J = 3.6 Hz), 3.81 (s, 9H), 2.84 (t, 2H, J = 7.2, 14.4 Hz), 2.25 (s, 3H), 1.93 (t, 2H, J = 7.2, 14.4 Hz), 1.22 (s, 6H).

Example B32: *N*-(2,6-dimethoxyphenyl)-5-[(1,1,3,3,6-pentamethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



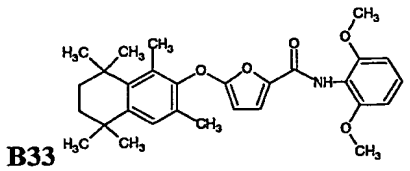
B32

Compound B32 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



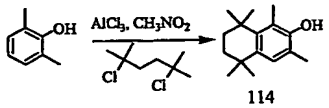
NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.33 (bs, 1H), 7.19 (t, 1H, J = 8.31, 8.35 Hz), 7.13 (d, 1H, J = 3.6 Hz), 6.96 (s, 1H), 6.81 (s, 1H), 6.62 (s, 1H), 6.59 (s, 1H), 5.34 (d, 1H, J = 3.4 Hz), 3.84 (s, 6H), 2.28 (s, 3H), 1.92 (s, 2H), 1.30 (s, 6H), 1.26 (s, 6H).

Example B33: *N*-(2,6-dimethoxyphenyl)-5-[(1,3,5,5,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide



B33

Compound B33 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was prepared according to the following method:



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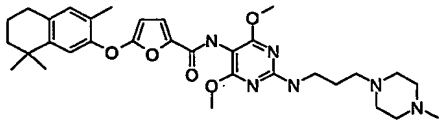
NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.35 (s, 1H), 7.20 (t, 1H, J = 9 Hz), 7.06 (d, 2H, J = 3 Hz), 6.63 (d, 2H, J = 9 Hz), 4.98 (d, 1H, J = 3 Hz), 3.86 (s, 6H), 2.36 (s, 3H), 2.17 (s, 3H), 1.66 (m, 4H), 1.40 (s, 6H), 1.28 (s, 6H).

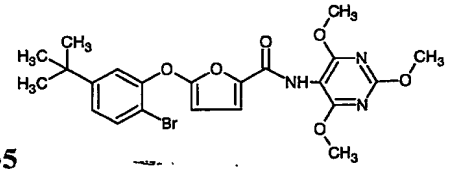
Example B34: N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide



B34

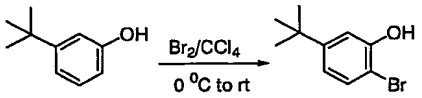
Compound B34 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting compounds and reaction conditions.

Example B35: 5-(2-bromo-5-tert-butylphenoxy)-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B35

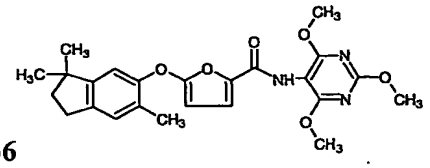
Compound B35 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



120

NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.54 (d, 1H, J = 6 Hz), 7.19-7.15 (m, 3H), 7.02 (bs, 1H), 5.46 (d, 1H, J = 3.6 Hz), 3.97 (s, 9H), 1.29 (s, 9H).

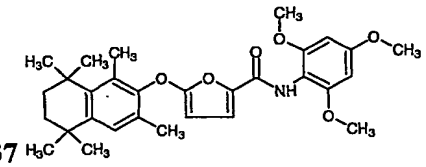
Example B36: N-(2,4,6-trimethoxy-5-pyrimidinyl)-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B36

Compound B36 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.13 (d, 1H, J = 3.6 Hz), 7.06 (s, 1H), 7.0 (bs, 1H), 6.83 (s, 1H), 5.30 (d, 1H, J = 3.6 Hz), 3.97 (s, 9H), 2.85 (t, 2H, J = 14.54 Hz), 2.24 (s, 3H), 1.93 (t, 2H, J = 7.18 Hz), 1.22 (s, 6H).

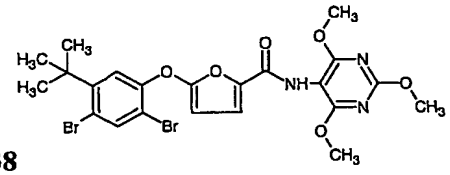
Example B37: 5-[(1,3,5,5,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-*N*-(2,4,6-trimethoxyphenyl)-2-furamide



B37

Compound B37 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.19 (s, 1H), 7.05 (s, 1H), 7.04 (d, 1H, J = 3.6 Hz), 6.19 (s, 2H), 4.96 (d, 1H, J = 3.6 Hz), 3.83 (s, 6H), 3.82 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H), 1.40 (s, 6H), 1.28 (s, 6H).

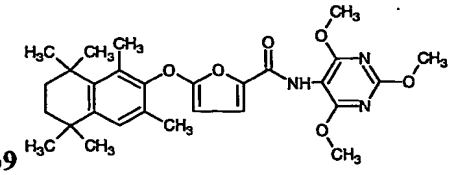
Example B38: 5-(2,4-dibromo-5-*tert*-butylphenoxy)-*N*-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



B38

Compound B38 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.85 (s, 1H), 7.23 (s, 1H), 7.16 (d, 1H, J = 3.6 Hz), 7.01 (bs, 1H), 5.51 (d, 1H, J = 3.6 Hz), 3.97 (s, 9H), 1.46 (s, 9H).

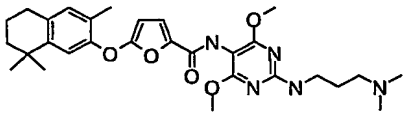
Example B39: 5-[(1,3,5,5,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-1-yl)oxy]-*N*-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



B39

Compound B39 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.07 (d, 1H, J = 3.8 Hz), 7.03 (s, 1H), 4.98 (d, 1H, J = 3.6 Hz), 3.99 (s, 6H), 3.98 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H), 1.66 (m, 4H, J = 1.32 Hz), 1.40 (s, 6H), 1.28 (s, 6H).

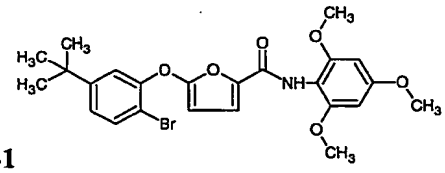
Example B40: N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxypyrimidin-5-yl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide



B40

Compound B40 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting compounds and reaction conditions.

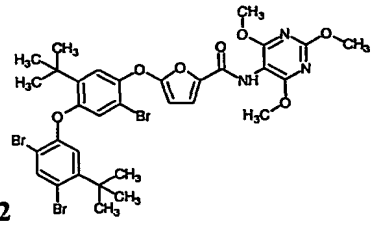
Example B41: 5-(2-bromo-5-*tert*-butylphenoxy)-*N*-(2,4,6-trimethoxyphenyl)-2-furamide



B41

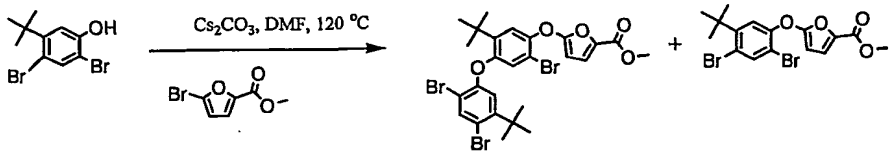
Compound B41 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.54 (d, 1H, J = 8.5 Hz), 7.18 (d, 1H, J = 3.6 Hz), 7.14-7.12 (m, 2H, J = 2.27, 4.72 Hz), 6.17 (s, 2H), 5.47 (d, 1H, J = 3.6 Hz), 3.81 (s, 9H), 1.28 (s, 9H).

Example B42: 5-[2-bromo-5-*tert*-butyl-4-(2,4-dibromo-5-tert-butylphenoxy)phenoxy]-*N*-(2,4,6-trimethoxypydrimidin-5-yl)-2-furamide



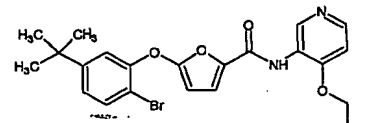
B42

Compound B42 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, DMSO – d_6): δ 9.24 (bs, 1H), 8.00 (s, 1H), 7.37 (s, 1H), 7.24 (d, 1H, J = 3.6 Hz), 7.06 (s, 2H), 7.00 (s, 1H), 5.64 (d, 1H, J = 3.6 Hz), 3.91 (s, 3H), 3.87 (s, 6H), 1.38 (s, 9H), 1.37 (s, 9H).

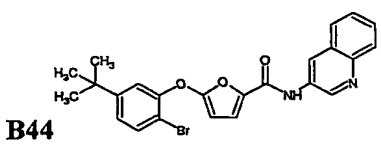
Example B43: 5-(2-bromo-5-*tert*-butylphenoxy)-*N*-(4-ethoxypyridin-3-yl)-2-furamide



B43

Compound B43 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 9.57 (bs, 1H), 8.30 (s, 1H), 8.27 (d, 1H, J = 5.48 Hz), 7.55 (d, 1H, J = 8.31 Hz), 7.21 (m, 2H), 7.15 (t, 1H, J = 2.17 Hz), 6.80 (d, 1H, J = 5.67 Hz), 5.46 (m, 1H), 4.20 (d, 2H, J = 13.98 Hz), 1.48 (dd, 3H, J = 13.98, 6.99 Hz), 1.28 (s, 9H).

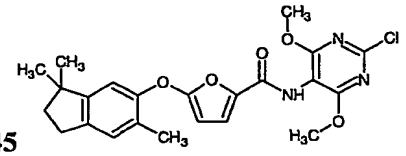
Example B44: 5-(2-bromo-5-*tert*-butylphenoxy)-*N*-quinolin-3-yl-2-furamide



B44

Compound B44 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 8.86 (t, 1H, J = 7.18 Hz), 806 (d, 1H, J = 8.31 Hz), 7.83 (d, 1H, J = 8.12 Hz), 7.65 (d, 1H, J = 8.31 Hz), 7.55 (ddd, 2H, J = 12.84, 8.31, 7.18 Hz), 7.27 (d, 1H, J = 3.59 Hz), 7.22 (m, 1H), 7.18 (d, 1H, J = 10.58 Hz), 5.47 (d, 1H, J = 3.6 Hz), 1.30 (s, 9H).

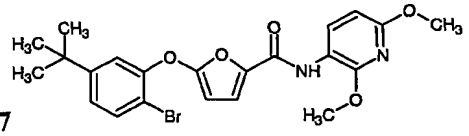
Example B45: *N*-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-2,3-dihydro-*1H*-inden-5-yl)oxy]-2-furamide



B45

Compound B45 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the desired title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.15 (d, 1H, J = 3.59 Hz), 7.07 (s, H), 6.83 (s, 1H), 5.29 (d, 1H, J 3.59 Hz), 4.01 (s, 6H), 2.85 (d, 2H, J = 10.01 Hz), 2.24 (s, 3H), 1.94 (t, 2H, J = 7.27 Hz), 1.22 (s, 6H).

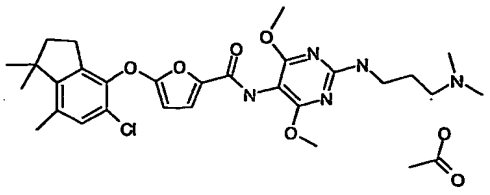
Example B47: 5-(2-bromo-5-tert-butylphenoxy)-N-(2,6-dimethoxypyridin-3-yl)-2-furamide



B47

Compound B47 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the title product were as follows: ^{1}H NMR (ppm, DMSO-d_6): δ 9.26 (s, 1H) 7.81 (d, 1H, J = 8.31 Hz), 7.67 (d, 1H, J = 8.69 Hz), 7.34 (d, 1H, J = 1.89 Hz), 7.27 (d, 2H, J = 8.69 Hz), 6.38 (d, 1H, J = 8.31 Hz), 5.64 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 1.25 (s, 9H).

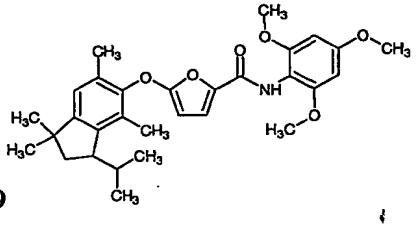
Example B48: 5-(5-Chloro-1,1,7-trimethyl-indan-4-yloxy)-furan-2-carboxylic acid [2-(3-dimethylamino-propylamino)-4,6-dimethoxy-pyrimidin-5-yl]-amide acetic acid salt



B48

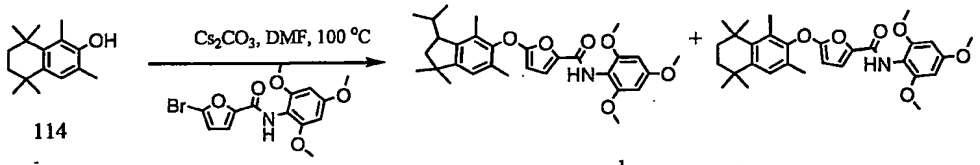
Compound B48 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

Example B49: 5-[(3-isopropyl-1,1,4,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-*N*-(2,4,6-trimethoxyphenyl)-2-furamide



B49

Compound B49 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



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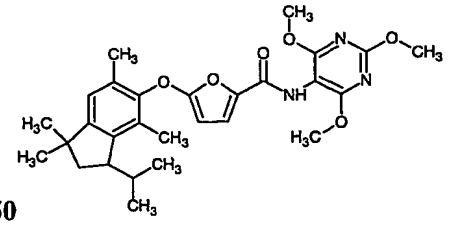
NMR data consistent with the title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.19 (s, 1H), 7.04 (d, 1H, J = 3.59 Hz), 6.81 (s, 1H), 6.19 (s, 2H), 4.92 (d, 1H, J = 3.59 Hz), 3.83 (s, 6H), 3.82 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.33(s, 3H), 1.15 (s, 3H), 0.96 (d, 3H, J = 6.80 Hz), 0.60 (d, 3H, J = 6.80 Hz).

Example B50: 5-[(3-isopropyl-1,1,4,6-tetramethyl-2,3-dihydro-1H-inden-5-yl)oxy]-*N*-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



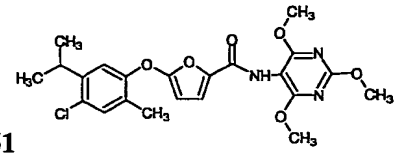
B50

Compound B50 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

NMR data consistent with the title product were as follows: ^{1}H NMR (ppm,

$CDCl_3$): δ 7.06 (d, 1H, J = 3.59 Hz), 7.03 (s, 1H), 6.80 (s, 1H), 3.98 (s, 6H), 3.97 (s, 3H), 4.92 (m, 1H), 2.90 (m, 2H, J = 19.83, 11.90, 11.52, 4.72 Hz), 2.18 (s, 3H), 2.16 (s, 3H), 1.84 (dt, 1H, J = 13.22, 8.88 Hz), 1.32 (s, 3H), 1.14 (s, 3H), 0.95 (m, 3H), 0.60 (d, 3H, J = 6.80 Hz).

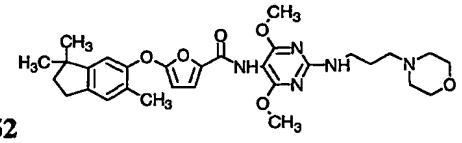
Example B51: 5-(4-chloro-5-isopropyl-2-methylphenoxy)-*N*-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



B51

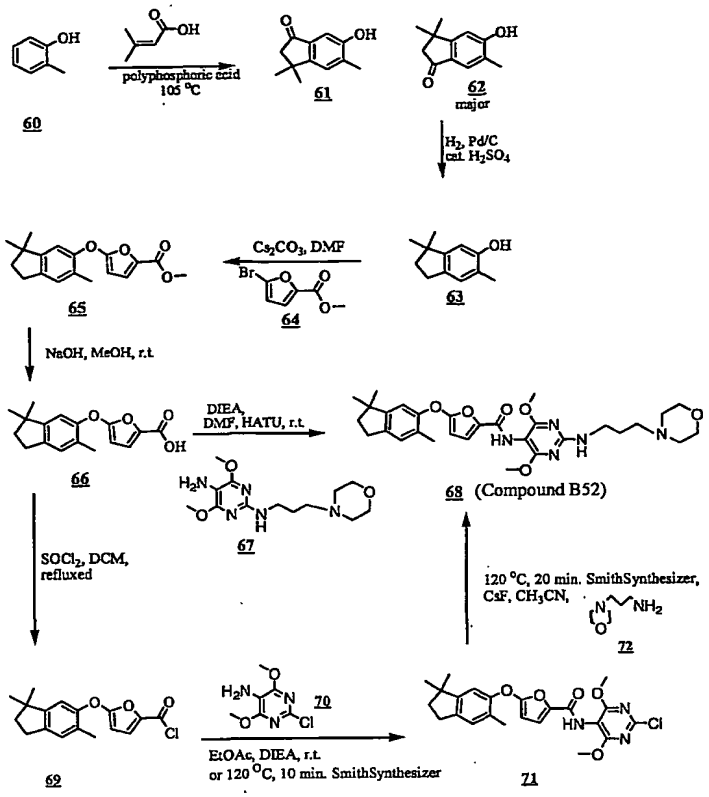
Compound B51 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the title product were as follows: ^1H NMR (ppm, $CDCl_3$): δ 7.24 (s, 1H), 7.14 (d, 1H, J = 3.40 Hz), 6.98 (s, 2H), 5.35 (d, 1H, J = 3.40 Hz), 3.97 (s, 9H), 3.33 (d, 1H, J = 6.80 Hz), 2.24 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H).

Example B52: *N*-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-5-[3,3,6-trimthyl-2,3-dihydro-*1H*-inden-5-yl)oxy]-2-furamide



B52

Compound B52 was synthesized according to a method analogous to Scheme B, using similar starting compounds and reaction conditions as shown and described below. NMR data consistent with the title product were as follows: ^1H NMR (ppm, $CDCl_3$): δ 7.09 (d, 1H, J = 3.40 Hz), 7.05 (s, 1H), 6.95 (s, 1H), 6.82 (s, 1H), 5.72 (bs, 1H), 5.29 (d, 1H, J = 3.40 Hz), 3.87 (s, 6H), 3.75 (dd, 4H, J = 9.07, 4.53 Hz), 3.47 (m, 2H), 2.84 (d, 2H, J = 7.18 Hz), 2.51 (d, 6H, J = 6.42 Hz), 2.23 (s, 3H), 1.93 (d, 2H, J = 7.18 Hz), 1.78 (t, 2H, J = 6.42 Hz), 1.21 (s, 6H).



5-hydroxy-3,3,6-trimethyl-1-indanone 62: To a three-necked round bottom flask assembled with a condenser, thermometer and mechanic stirrer under nitrogen, *o*-cresol (1197 mmol, 124 ml) and 3,3-dimethylacrylic acid (1520 mmol, 154 g) were added. The mixture was gently stirred and heated at 40 °C while adding polyphosphoric acid (3.9 L). After the addition of polyphosphoric acid was completed, the contents were rapidly heated to 105 °C, and the heating mantel was removed. The reaction mixture was monitored by TLC (1:3 ethyl acetate: hexane) showing no starting materials. The reaction was quenched by pouring the hot mixture into a large bucket of ice water with constant stirring. The aqueous layer was extracted with ethyl acetate. The organic phase was concentrated, and the crude product was crystallized with ethyl acetate to obtain pure Compound 62 (21 g, 9.5 %). NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.83 (s, 1H), 6.06 (bs, 1H), 2.55 (s, 2H), 2.27 (s, 3H), 1.36 (s, 6H).

3,3,6-trimethyl-5-indanol 63:A solution of 5-hydroxy-3,3,6-trimethyl-1-indanone (21.5 mmol, 4.1 g) and sulfuric acid (290 ul) in methanol (150 ml) were

degassed with nitrogen for at least twenty minutes following by the addition of catalyst palladium on carbon (4.3 mmol, 0.63 g). The ketone was reduced under 40 psi of H_2 overnight. The contents were filtered over celite. Methanol was removed in vacuum to give brown oil residue that was redissolved in ethyl acetate and washed with water until neutral and brine. The organic layer was dried over sodium sulfate and brought to dryness given light yellow oil. The crude product was purified by plug column chromatography (1:3 ethyl acetate: hexane) to give light yellow solid Compound 63 (3.6 g, 93%). NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.57 (s, 1H), 4.58 (s, 1H), 2.78 (t, 2H), 2.21 (s, 3H), 1.89 (t, 2H), 1.21 (s, 6H).

Methyl 5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furoate 65: In a one-necked round-bottom flask assembled with a condenser and gas outlet, a solution of 63 (22.73 mmol, 4.0 g), 64 (17.6 mmol, 3.6 g) and cesium carbonate (22.8 mmol, 7.4 g) in DMF (45 mL) was degassed with nitrogen gas for 20 minutes then heated to 100 °C for 7 hours under N_2. The mixture was cooled down to room temperature and quenched with 1M HCl. The content was extracted with ethyl acetate, water and brine. The organic phase was dried over sodium sulfate. The crude product was purified by plug column chromatography (1:5 ethyl acetate: hexane) to obtain yellow oil Compound 65 (5.8 g, 84%). Note: The material from the baseline of the column was 66. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.89 (t, 2H), 2.20 (s, 3H), 2.77 (t, 2H), 3.86 (s, 3H), 5.22 (d, 2H), 6.56 (s, 1H), 6.93 (s, 1H), 7.12 (d, 1H), APCI-MS m/z 302.2 $(M+H)^+$.

5[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furoic acid 66: To a solution of 65 (19.3 mmol, 5.8 g) in methanol (10 ml) in a one-necked round bottom flask assembled with a stir bar, 4M NaOH aqueous solution (20 ml) was added. The contents were stirred at room temperature overnight. The clear brown solution was acidified with 2M HCl and stirred for 3 hours. The aqueous layer was extracted with ethyl acetate and brine then dried over sodium sulfate. The crude product was crystallized with CH_3CN to give pure light yellow solid Compound 66 (3.18 g, 57 %). NMR data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$, ppm): δ 7.26 (d, 1H), 7.05 (s, 1H), 6.85 (s, 1H), 2.84 (t, 2H), 2.20 (s, 3H), 1.93 (t, 2H), 1.21 (s, 6H).

N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide 68 (Compound B52): Procedure 1: To a solution of 66 (9.74 mmol, 2.8 g), 67 (8.0 mmol, 2.4g) and HATU (10.2 mmol, 3.4 g) in DMF (18 ml) prepared in a one-necked flask assembled with a gas outlet and a stir bar, diisopropylethylamine (33.5 mmol, 6 ml) was added slowly via a syringe under N_2. The reaction mixture was stirred under N_2 overnight. The solvent was removed under vacuum pressure then purified by HPLC (32_95_70 min. – CH_3CN: 0.1M NH_4oAC) without further work-up to give white solid product 68 (2.84 g, 52%). Compound 68 was dissolved in methylene chloride and then dried in vacuum, yielding an amorphous solid. NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 17.10 (d, 1H), 7.05 (s, 1H), 6.95 (s, 1H), 6.82 (s, 1H), 5.72 (bs, 1H), 5.29 (d, 1H), 3.87 (s, 6H), 3.75 (t, 4H), 3.48 (bt, 2H), 2.84 (t, 2H), 2.49 (m, 6H), 2.23 (s, 3H), 1.93 (t, 2H), 1.81 (t, 4H), 1.21 (s, 6H).

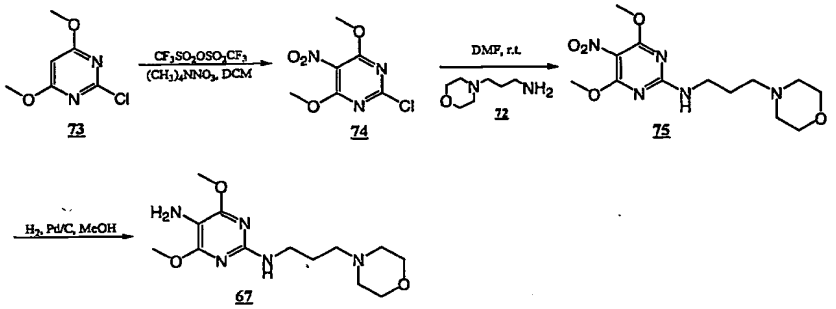
Procedure 2: Compound 68 was also be synthesized from 71. In a 5 ml microwave tube assembled with a stir bar, *N*-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy]-2-furamide 71(0.35 g, 0.76 mmol), cesium fluoride (0.29 g, 1.9 mmol), acetonitrile (3.8 ml) and amine (0.14 g, 0.91 mmol) were added. The mixture was heated to 120 °C for 20 minutes by Smith Synthesizer. Without work-up the crude product was purified by HPLC.

5-[(3,3,6-trimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy]-2-furoyl chloride 69: In a one-necked round bottom flask assembled with a stir bar, condenser and gas inlet was added 5[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furoic acid 66 (18.6 mmol), thionyl chloride (6 ml), and methylene chloride (100 ml). The mixture was refluxed overnight. After cooling down to room temperature, the contents were washed with water and brine to quench the excess thionyl chloride. Organic solution was dried over Na_2SO_4. Reddish-brown oil product was passed over a short silica gel plug with 1:1 (ethyl acetate: hexane). NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.22 (s, 6H), 1.91-197 (m, 2H), 2.19 (s, 3H), 2.85 (t, 2H), 5.31 (d, 1H), 6.86 (s, 1H), 7.07 (s, 1H), 7.45 (d, 1H).

***N*-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy]-2-furamide 71:** 5-[(3,3,6-trimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy]-2-furoyl chloride 69 (2.66 g, 8.71 mmol) and 2-chloro-4,6-

dimethoxypyrimidin-5-amine (1.65 g, 8.71 mmol) were added into a 25-ml round-bottom flask containing a stir bar and ethyl acetate (17.5 ml) following by slow addition of diisopropylethyl amine (3.2 ml). The mixture was stirred at room temperature overnight. An alternate route was to heat the mixture to 120 degree Celsius for 10 minutes by Smith Synthesizer microwave. Classical work up was carried out. Crude product was purified by flask chromatography (silica gel 1:5 ethyl acetate: hexane). Light brown product 71 was obtained (0.5 g, 13%). NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.22 (s, 6H), 1.94 (t, 2H), 2.24 (s, 3H), 2.85 (t, 2H), 4.01 (s, 6H), 5.30 (d, 1H), 6.83 (s, 1H), 7.08 (d, 2H), 7.15 (d, 1H).

Compound 67 was synthesized according to the nitration scheme below:



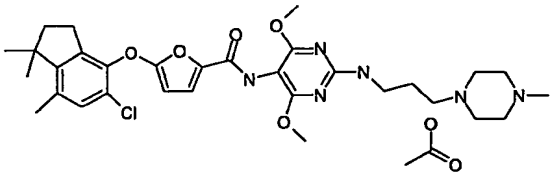
2-chloro-4,6-dimethoxy-5-nitropyrimidine 74: In a 12-L flask assembled with an overhead stirrer, thermometer, N_2 inlet and addition funnel, tetramethylammonium nitrate (587 g, 4.31 mol) and dichloromethane (4 L) were added. The contents were stirred under N_2 for 1 hour at room temperature (20°C). Triflic anhydride (1.216 g, 4.31 mol, 725 ml) was added dropwise over a period of 45 minutes so that the temperature remained below 25°C. The addition funnel was rinsed with 100 ml of dichloromethane, and the dichloromethane was added to the reaction. The contents were stirred at room temperature under N_2 for 2 hours. The reaction mixture was then cooled to –78°C in a dry ice/acetone bath. The 2-chloro-4,6-dimethoxypyrimidine 73 (500 g, 2.87 mol) was dissolved in minimal amount of dichloromethane (3L). The solution of 73 was added dropwise over a period of 1.5 hours. The addition rate was important to ensure the temperature did not rise above 5°C. After the addition of solution 73, the addition funnel was rinsed with 100 ml of dichloromethane and the rinse was added to the reaction. The acetone/dry bath was removed and the reaction was stirred for 38 hours under N2 as it warmed to room temperature. The reaction was monitored by TLC (3:1 CHCL3: Hexanes) and

quenched by pouring reaction mixture into ~2 kg of ice. The contents were neutralized with $NaHCO_3$ aqueous solution (pH = 8) and the dichloromethane layer was separated. The aqueous layer was extracted with 3x100 ml of dichloromethane. The dichloromethane portions were combined and washed with 2x1L of H_2O. The combined dichloromethane portion was dried over MgSO4, and brought to dryness. Compound 74 was a white solid (615 g, 98 %).

4,6-dimethoxy-N-(3-morpholin-4-ylpropyl)-5-nitropyrimidine-2-amine 75: A mixture of 2-chloro-4,6-dimethoxy-5-nitropyrimidine 74 (92.32 mmol, 20.2 g) in DMF (23 ml) was cooled down to 0°C. 4-(3-Aminopropyl) morpholine 72 (92.4 mmol, 13.5 ml) was added drop by drop via a syringe into the mixture 74. The contents were warmed up to room temperature and stirred overnight under N_2. The organic solvents were removed by high vacuum, and the crude product was purified by flash column chromatography (2:5 methanol: ethyl acetate) without aqueous work up. Compound 75 had bright yellow solid (18 g, 60 %).

N-(5-amino-4,6-dimethoxy-2-pyrimidinyl)-N-(3-(4-morpholinyl)propyl]amine 67: A solution of 4,6-dimethoxy-N-(3-morpholin-4-ylpropyl)-5-nitropyrimidine-2-amine 75 (55 mmol, 18 g) in methanol (500 ml) was degassed for 15 minutes followed by the addition of catalyst Pd/C (5.5 mmol, 0.8 g). The nitro-group was reduced under 30 psi of H_2 overnight. The contents were filtered over Celite, and the organic solvent was removed in vacuum. The product was dried under high vacuum to give brown solid Compound 67 (15 g, 90 %).

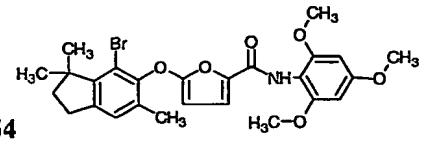
Exapample B53: 5-[(5-chloro-1,1,7-trimethyl-2,3-dihydro-1H-inden-4-yl)oxy]-N-(4,6-dimethoxy-2{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-2-furamide Acetic acid Salt



B53

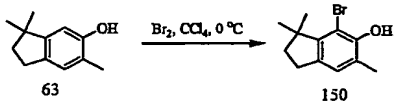
Compound B53 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

Example B54: 5-[(4-bromo-3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-*N*-(2,4,6-trimethoxyphenyl)-2-furamide



B54

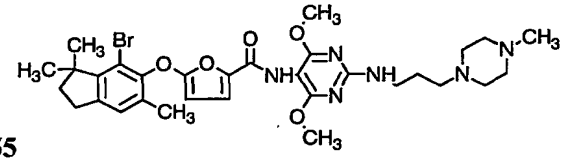
Compound B54 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was prepared according to the following method:



63 150

NMR data consistent with the title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.20 (bs, 1H), 7.05 (d, 1H, J = 3.40 Hz), 7.00 (s, 1H), 6.18 (s, 2H), 5.04 (d, 1H, J = 3.78 Hz), 3.83 (s, 6H), 3.82 (s, 3H), 2.85 (t, w2H, J = 7.55 Hz), 2.23 (s, 3H), 1.98 (dd, 2H, J = 14.73, 7.55 Hz), 1.42 (s, 6H).

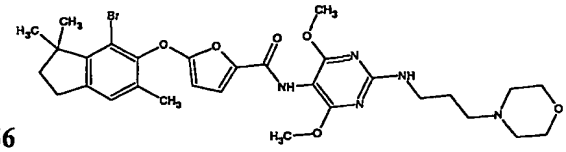
Example B55: 5-[(4-bromo-3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-*N*-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-2-furamide



B55

Compound B55 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR data consistent with the title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.04 (d, 1H, J = 3.78 Hz), 7.00 (s, 1H), 6.97 (s, 1H), 5.70 (bs, 1H) 5.03 (d, 1H, J = 3.78 Hz), 3.89 (s, 6H), 3.46 (d, 2H, J = 5.29 Hz), 2.85 (dd, 2H, J = 14.73, 7.18 Hz), 2.56 (dd, 8H, J = 7.55, 6.80 Hz), 2.35 (s, 3H), 2.22 (s, 3H), 1.98 (t, 2H, J = 7.55 Hz), 1.79 (d, 2H, J = 6.42 Hz), 1.42 (s, 6H).

Example B56: 5-[(4-bromo-3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-*N*-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-2-furamide

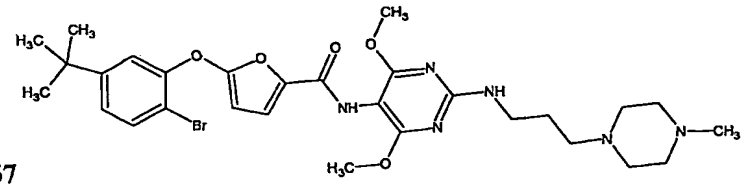


B56

Compound B56 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

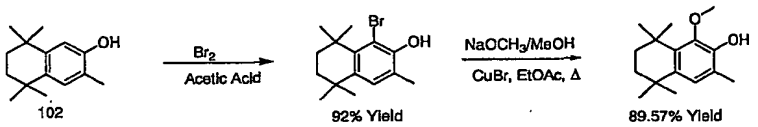
NMR data consistent with the title product were as follows: ^{1}H NMR (ppm, $CDCl_3$): δ 7.13 (s, 1H), 7.08 (d, 1H, J = 3.40 Hz), 7.01 (s, 1H), 5.78 (bs, 1H), 5.05 (d, 1H, J = 3.78 Hz), 3.90 (s, 10H), 3.53 (s, 2H), 3.06 (s, 6H) 2.84 (t, 2H, J = 7.18 Hz), 2.22 (s, 3H), 1.95 (d, 4H, J = 7.55 Hz), 1.41 (s, 6H).

Example B57: 5-(2-bromo-5-*tert*-butylphenoxy)-*N*-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-2-furamide



B57

Compound B57 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following method:



102 — 92% Yield, 105 — 89.57% Yield, 121

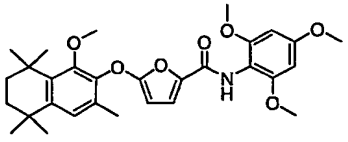
1-Bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol: In a 500 mL round bottom flask, 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol (10.2 g, 46.72 mmol) was dissolved in 100mL acetic acid. To this solution Bromine (8.2 g, 51.39 mmol) was added. The reaction was stirred at room temperature for 20 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel chromatography eluted with hexane to yield 1-Bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol (12.8 g, 92% yield). NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 6H), 1.52 (s, 6H), 1.58-1.63 (m, 2H), 1.68-1.71 (m, 2H), 2.25 (s, 3H), 5.99 (s, 1H), 7.05 (s, 1H).

1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol: In 1000 mL round-bottom flask, 1-bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol (12.8 g, 43.06 mmol) and Sodium methoxide in methanol (5.0 M) were combined. To this solution CuBr (1.24 g, 8.61mmol) was added followed by ethyl acetate (2.5 mL). The reaction was stirred and heated to reflux for 16 hours. The reaction mixture was cooled to room temperature then poured into water and extracted

with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate and concentrated to yield 1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol (9.58 g, 90% yield). NMR data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.25 (s, 6H), 1.39 (s, 6H), 1.52-1.61 (m, 4H), 2.21 (s, 3H), 3.81 (s, 3H), 5.08 (s, 1H), 7.01 (s, 1H).

5-[(1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furoic acid: 1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol (2.0 g, 8.05 mmol), methyl 5-bromo-2-furoate (1.65 g, 8.05 mmol), and Cs_2CO_3 were dissolved in DMF (20 mL). The solution was placed under nitrogen, stirred and heated to 70°C overnight. The cooled reaction mixture was poured into water, acidify with 6N HCl (100 mL) and extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel chromatography eluted with hexane/ethyl acetate (2:1 v/v) to yield 5-[(1-methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furoic acid (1.1 g, 37 % yield). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 1.35 (s, 6H), 1.60 (m, 4H), 2.17 (s, 3H), 3.84 (s, 3H), 5.09 (d, 1H), 6.92 (s, 1H), 7.24 (d, 1H), APCI-MS *m/z* 373.1 $(M+H)^+$. NMR data consistent with the title product were as follows: ^{1}HNMR (ppm, $CDCl_3$): δ 7.53 (d, 1H, J = 8.31 Hz), 7.17 (d, 1H, J = 1.89 Hz), 7.13 (d, 2H, J = 5.29 Hz), 6.97 (s, 1H), 5.71 (bs, 1H), 5.44 (d, 1H, J = 3.40 Hz), 3.87 (s, 6H), 2.57 (dd, 8H, J = 13.60, 6.80 Hz), 2.36 (s, 3H), 2.10 (d, 4H, J = 18.89 Hz), 1.78 (d, 2H, J = 13.22 Hz), 1.28 (s, 9H).

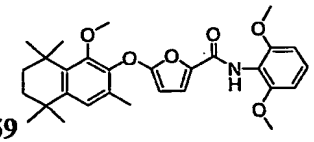
Example B58: 5-[(1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B58

Compound B58 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.29 (s, 6H), 1.39 (s, 6H), 1.68 (m, 4H), 2.22 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 3.88 (s, 3H), 5.10 (d, 1H), 6.29 (s, 2H), 7.05 (s, 1H), 7.11 (d, 1H), APCI-MS *m/z* 524 $(M+H)^+$.

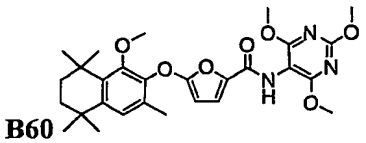
le B59: N-(2,6-dimethoxyphenyl)-5-[(1-methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide



B59

Compound B59 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (acetonitrile-d3): δ 1.29 (s, 6H), 1.38 (s, 6H), 1.67 (s. 4H), 2.25 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 5.15 (d, 1H), 6.71 (s, 1H), 6.73 (s, 1H), 7.03 (d, 1H), 7.09 (s, 1H), 7.29 (t, 1H) 7.62 (s, 1H), APCI-MS *m/z* 494 $(M+H)^+$.

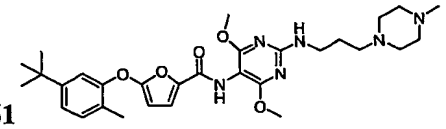
Example B60: 5-[(1-methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-N-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



B60

Compound B60 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 1.20 (s, 6H), 1.29 (s, 6H), 1.58 (d, 4H, J = 2.27 Hz), 2.11 (s, 3H), 3.78 (s, 3H), 3.89 (s, 6H), 3.91 (s, 3H), 5.01 (d, 1H, J = 3.78 Hz), 6.95 (s, 1H), 7.03 (d, 1H, J = 3.40 Hz), APCI-MS *m/z* 526 $(M+H)^+$.

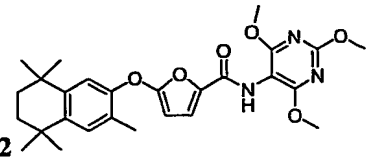
Example B61: 5-[5-(tert-butyl)-2-methylphenoxy]-N-(4,6-diemthoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-2-furamide



B61

Compound B61 was synthesized in a manner analogous to that of B1, according to Scheme B (HBTU coupling), using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H), 1.80 (m, 6H), 2.26 (s, 3H), 2.50 (s, 3H), 2.60 (br m, 6H), 3.64 (t, 2H), 3.88 (s, 61H), 5.35 (d, 1H), 5.82 (t, 1H), 6.98 (s, 1H), 7.10 (s and d, 2H), 7.17 (m, 2H), APCI-MS *m/z* 567.2 $(M+H)^+$.

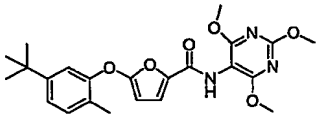
Example B62: 5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B62

Compound B62 was synthesized in a manner analogous to that of B1, according to Scheme B (HBTU coupling), using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.23 (s, 6H), 1.27 (s, 6H), 1.69 (s, 4H), 2.22 (s, 3H), 3.95 (s, 6H), 3.98 (s, 3H), 5.34 (d, 1H), 7.02 (s, 1H), 7.14 (d, 1H), 7.23 (s, 1H), APCI-MS *m/z* 496.5 $(M+H)^+$.

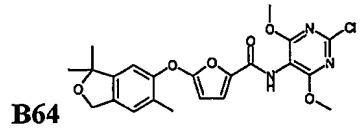
Example B63: 5-(5-tert-butyl-2-methylphenoxy)-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B63

Compound B63 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9H), 2.24 (s, 3H), 3.95 (s, 6H), 3.98 (s, 3H), 5.36 (d, 1H), 7.12 (s, 1H), 7.15 (d, 1H), 7.22 (m, 2H), APCI-MS *m/z* 442.1 $(M+H)^+$.

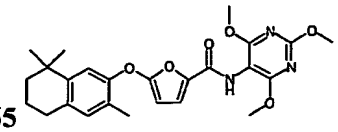
Example B64: *N*-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B64

Compound B64 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 6H), 2.29 (s, 3H), 4.01 (s, 6H), 5.02 (s, 2H), 5.37 (d, 1H, J = 3.40 Hz), 6.81 (s, 1H), 7.08 (s, 1H), 7.16 (d, 1H, J = 3.59 Hz).

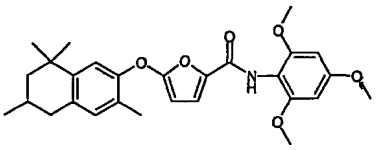
Example B65: N-(2,4,6-trimethoxy-5-pyrimidinyl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B65

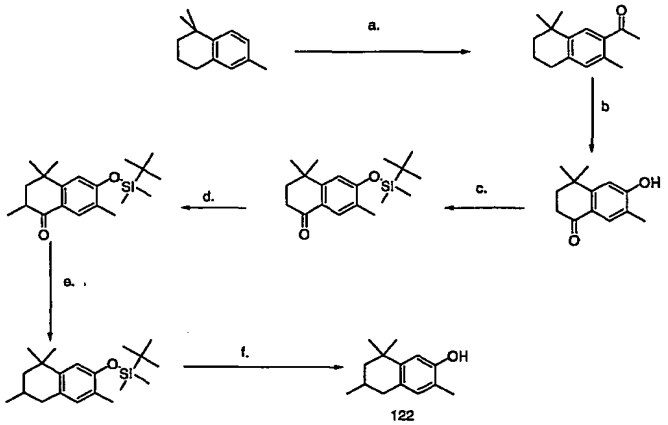
Compound B65 was synthesized in a manner analogous to that of B1, according to Scheme B (HBTU coupling), using similar starting compounds and reaction conditions. Yield of purified product was 33%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.24 (s, 6H), 1.68 (m, 2H), 1.78 (m, 2H), 2.19 (s, 3H), 2.72 (t, 2H, J = 6.32 Hz), 3.95 (s, 6H), 3.98 (s, 3H), 5.29 (d, 1H, J = 3.59 Hz), 6.96,(d, 1H,), 7.06 (s, 1H), 7.14 (d, 1H, J = 3.59 Hz), Mass APCI 468.5.

Example B66: 5-[(3,6,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B66

Compound B66 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following method:

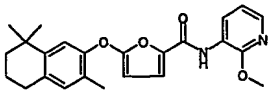


a. $AlCl_3$, AcylChloride, CH_3NO_2,0°C, 7 hrs.
b. McPBA, $NaHCO_3$(aq), CH_2Cl_2, air 423-120
c. TBDMS, DMF, Imidazole
d. 1. LDA, -78°C, THF, 30 min
2. MeI, 12h, RT
e. hydrogentation
f. acid

NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (dmso-d6): δ 1.00 (d, 3H, J = 6.42 Hz), 1.14 (s, 3H), 1.21 (s, 3H), 1.29 (d,

1H, J = 12.65 Hz), 1.57 (d, 1H, J = 13.03 Hz), 1.87 (s, 1H), 2.14 (s, 3H), 2.25 (dd, 1H, J = 12.09, 8.50 Hz), 2.72 (d, 1H, J = 16.43 Hz), 3.72 (s, 6H), 3.79 (s, 3H), 5.40 (d, 1H, J = 3.40 Hz), 6.26 (s, 2H), 6.97 (s, 1H), 7.11(s, 1H), 7.17 (d, 1H, J = 3.21 Hz), 8.90 (s, 1H), APCI mass 480.2.

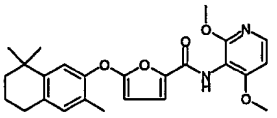
Example B67: N-(2-methoxy-3-pyridinyl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B67

Compound B67 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.23 (s, 6H), 1.66 (m, 2H), 1.81 (m, 2H), 2.19 (s, 3H), 2.72 (t, 2H, J = 6.23 Hz), 4.03(s, 3H), 5.34 (d, 1H, J = 3.59 Hz), 6.96 (m, 2H, J = 5.10, 4.91, 3.02, 1.89 Hz), 7.09 (s, 1H), 7.22 (d, 1H, J = 3.59 Hz), 7.89 (td, 1H, J = 5.10, 1.70 Hz), 8.42 (dd, 1H, J = 7.74, 1.70 Hz), APCI mass 407.2.

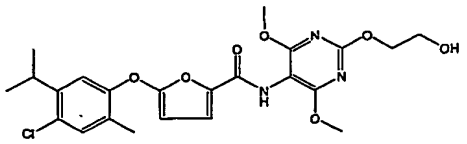
Example B68: N-(2,4-dimethoxy-3-pyridinyl)-5-[(3,8,8-trimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B68

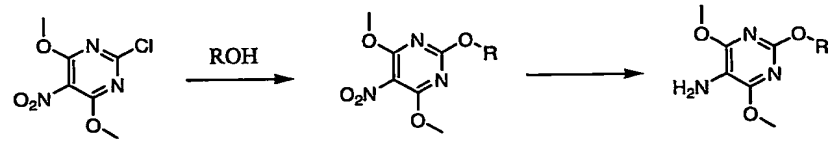
Compound B68 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.44 (s, 6H), 1.85 (m, 2H), 2.00 (m, 2H), 2.43 (s, 3H), 2.92 (t, 2H, J = 6.33 Hz), 4.10 (s, 3H), 4.18 (s, 3H), 5.50 (d, 1H, J = 3.59 Hz), 6.81 (d, 1H, J = 5 .85 Hz), 7.14 (s, 1H), 7.35 (d, 1H, J = 3.59 Hz), 7.47 (s, 1H), 8.22 (d, 1H, J = 5.85 Hz), APCI mass 437.2.

Example B69: 5-(4-chloro-5-isopropyl-2-methylphenoxy)-N-[2-(2-hydroxyethoxy)-4,6-dimethoxy-5-pyrimidinyl]-2-furamide



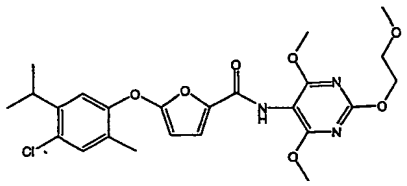
B69

Compound B69 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.19 (d, 6H, J = 7.18 Hz), 2.24 (s, 3H), 3.33 (dq, 1H, J = 7.18, 6.80 Hz), 3.97 (m, 8H), 4.48 (dd, 2H, J = 4.91, 4.53 Hz), 5.35 (d, 1H, J = 3.40 Hz), 6.97 (s, 1H), 7.02 (s, 1H), 7.14 (d, 1H, J = 3.78 Hz), 7.25 (m, 1H), APCI Mass 492.1.

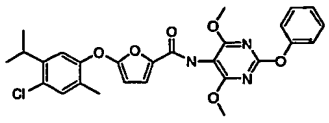
Example B70: 5-(4-chloro-5-isopropyl-2-methylphenoxy)-N-[4,6-dimethoxy-2-(2-methoxyethoxy)pyrimidin-5-yl]-2-furamide



B70

Compound B70 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.16 (d, 6H, J = 6.80 Hz), 2.23 (s, 3H), 3.33 (m, 1H, J = 6.80, 6.80, 6.80, 6.80 Hz), 3.42 (s, 3H), 3.76 (t, 2H, J = 4.91 Hz), 3.96 (s, 6H), 4.50 (dd, 2H, J = 5.29, 4.91 Hz), 5.34 (d, 1H, J = 3.40 Hz), 6.99 (s, 2H), 7.14 (d, 1H, J = 3.78 Hz), 7.23 (s, 1H), APCI Mass 506.1.

Example B71: 5-(4-chloro-5-isopropyl-2-methylphenoxy)-N-(4,6-dimethoxy-2-phenoxypyrimidin-5-yl)-2-furamide

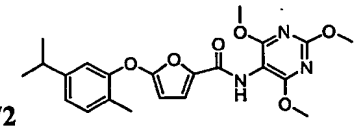


B71

Compound B71 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions.

NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.19 (d, 6H, J = 7.18 Hz), 2.24 (s, 3H), 3.34 (m, 1H, J = 7.18, 6.80, 6.80, 6.42 Hz), 3.85 (s, 6H), 5.35 (d, 1H, J = 3.40 Hz), 6.98 (s, 1H), 6.99 (s, 1H), 7.02 (s, 1H), 7.14 (d, 1H, J = 3.40 Hz), 7.21 (d, 2H, J = 8.31 Hz), 7.37 (d, 1H, J = 8.31 Hz), 7.39 (dd, 1H, J = 8.31, 7.18 Hz), APCI Mass 522.2.

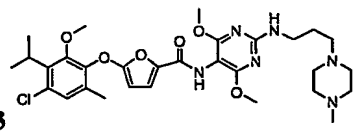
Example B72: 5-(5-isopropyl-2-methylphenoxy)-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B72

Compound B72 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d), 2.27 (3H, s), 2.87 (1H, hep), 3.94 (9H, s), 5.35 (1H, d), 6.93 (1H, s), 7.02 (2H, br s), 7.15 (2H, m), FI-PCI m/z 428.2 $(M+H)^+$.

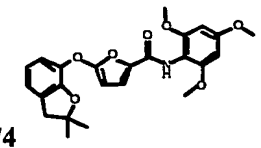
Example B73: 5-(4-chloro-3-isopropyl-2-methoxy-6-methylphenoxy)-N-(4,6-dimethoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-2-furamide



B73

Compound B73 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.34 (6H, d), 1.78 (2H, m), 2.19 (3H, s), 2.31 (3H, s), 2.51 (10H, br m), 3.38 (2H, m), 3.55 (1H, hep), 3.83 (3H, s), 3.89 (6H, s), 5.10 (1H, d, J = 4.8 Hz), 5.82 (1H, br t), 6.88 (1H, s, amide NH), 7.01 (1H, s), 7.06 (1H, d, J = 4.8 Hz), FI-PCI m/z 618.4, 619.4 $(M+H)^+$.

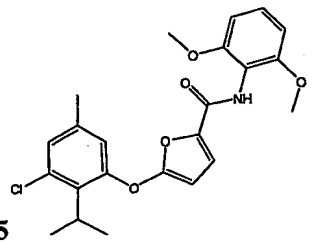
Example B74: 5-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B74

Compound B74 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The yield of the purified product was 41%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 6H), 3.12 (s, 2H), 3.80 (s, 9H), 5.48 (d, 1H), 6.20 (s, 2H), 6.81 (t, 1H), 6.98 (dd, 2H), 7.15 (d, 1H), 7.20 (br s, 1H), APCI-MS *m/z* 440.1 $(M+H)^+$.

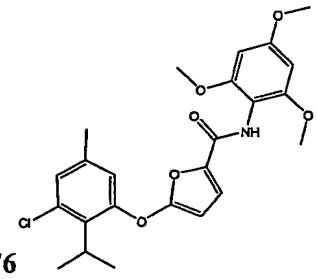
Example B75: 5-(3-chloro-2-isopropyl-5-methylphenoxy)-N-(2,6-dimethoxyphenyl)-2-furamide



B75

Compound B75 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.27 (s, 3H), 2.34 (s, 3H), 3.28 (septet, 1H, J = 9Hz), 3.87 (s, 6H), 5.44 (d, 1H, J = 3Hz), 6.62 (s, 1H), 6.65 (s, 1H), 6.95 (s, 1H), 7.17 (d, 1H), 7.23 (t, 1H), 7.31 (s, 1H), 7.37 (s, 1H), APCI-MS *m/z* 430.1 $(M+H)^+$.

Example B76: 5-(3-chloro-2-isopropyl-5-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

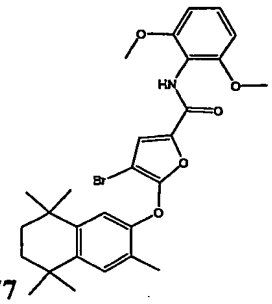


B76

Compound B76 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows:

^{1}HNMR (300 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.26 (s, 3H), 2.34 (s, 3H), 3.27 (septet, 1H, J = 9 Hz, J = 6 Hz), 5.44 (d, 1H, J = 3 Hz), 6.20 (s, 2H), 6.94 (s, 1H), 7.16 (d, 1H, J = 6 Hz), 7.23 (s, 1H), 7.30 (s, 1H), APCI-MS *m/z* 460.2 $(M+H)^+$.

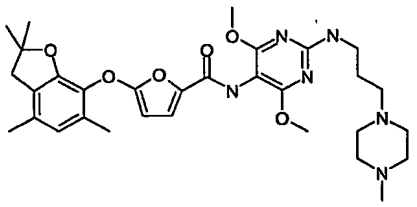
Example B77: 4-bromo-N-(2,6-dimethoxyphenyl)-5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B77

Compound B77 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (s, 6H), 1.24 (s, 6H), 1.61 (s, 4H), 2.26 (s, 3H), 3.72 (s, 6H), 6.70 (d, 2H), 6.81 (s, 1H), 7.21 (t, 1H), 7.26 (s, 1H), 7.46 (s, 1H), 9.25 (s, 1H), APCI-MS m/z 498.3 $(M+H)^+$.

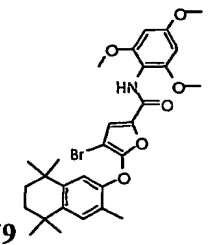
Example B78: N-(4,6-dimethoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-5-[(2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-7-yl)oxy]-2-furamide



B78

Compound B78 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

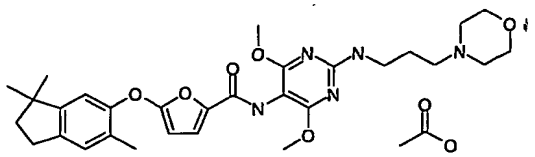
Example B79: 4-bromo-5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-n-(2,4,6-trimethylphenyl)-2-furamide



B79

Compound B79 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, DMSO-d_6): δ 1.15 (s, 6H), 1.22 (s, 6H), 1.60 (s, 4H), 2.25 (s, 3H), 3.69 (s, 6H), 3.78 (s, 3H), 6.28 (s, 2H), 6.82 (s, 1H), 7.24 (s, 1H), 7.43 (s, 1H), 9.08 (s, 1H), APCI-MS m/z 572.4 $(M+H)^+$.

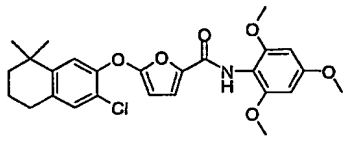
Example B80: N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide acetate



B80

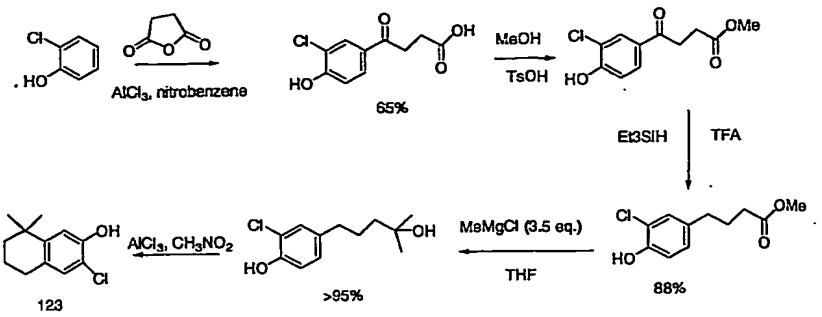
Compound B78 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

Example B81: 5-[(3-chloro-8,8-dimethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



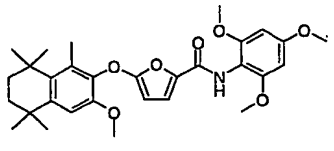
B81

Compound B81 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following method:



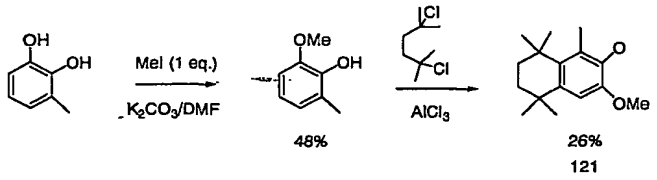
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.21 (s, 6H), 1.61 (m, 2H), 1.73 (m, 2H), 2.71 (t, 2H), 3.71 (s, 6H), 3.78 (s, 3H), 5.51 (d, 1H), 6.26 (s, 2H), 7.18 (s, 1H), 7.29 (s, 1H), 7.37 (s, 1H), 8.92 (s, 1H), APCI-MS *m/z* 486.3 $(M+H)^+$.

Example B82: 5-[(3-methoxy-1,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



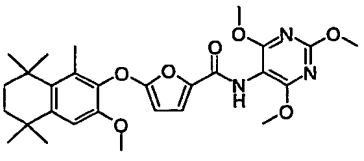
B82

Compound B82 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following method:



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.24 (s, 6H), 1.39 (s, 6H), 1.66 (s, 3H), 3.76 (s, 9H), 3.82 (s, 3H), 5.10 (d, 1H), 6.37 (s, 2H), 7.14 (s, 1H), 7.48 (d, 1H), 8.94 (s, 1H), APCI-MS *m/z* 524.3 $(M+H)^+$.

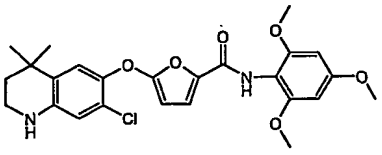
Example B83: 5-[(3-methoxy-1,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B83

Compound B83 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.27 (s, 6H), 1.34 (s, 6H), 1.61 (s, 4H), 2.30 (s, 3H), 3.71 (s, 3H), 3.86 (s, 6H), 3.90 (s, 3H), 5.08 (d, 1H), 6.94 (s, 1H), 7.09 (d, 1H), 9.14 (s, 1H), APCI-MS *m/z* 526.3 $(M+H)^+$.

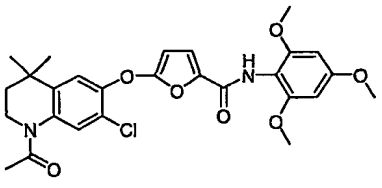
Example B84: 5-[(7-chloro-4,4-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B84

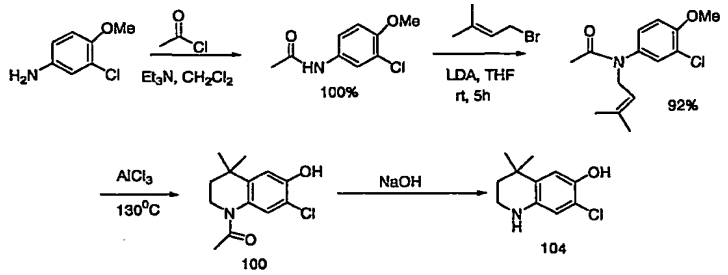
Compound B84 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (CDCl3): δ 1.25 (s, 6H), 1.71 (t, 2H), 3.31 (t, 2H), 3.81 (s, 9H), 5.22 (d, 1H), 6.18 (s, 2H), 6.50 (s, 1H), 7.06 (s, 1H), 7.08 (d, 1H), 7.19 (s, 1H), APCI-MS *m/z* 487.2 $(M+H)^+$.

Example B85: 5-[(1-acetyl-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



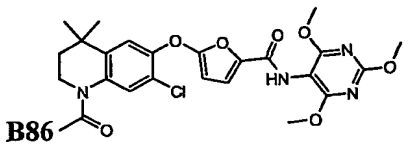
B85

Compound B85 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. The requisite phenol was synthesized as follows:



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 1.78 (t, 2H, J = 6.318 Hz), 2.28 (s, 3H), 3.76(t, 2H), 3.78 (s, 9H), 5.48 (d, 1H, J = 3.546 Hz), 6.17 (s, 2H), 7.13 (s, 2H), 7.15 (s, 1H), APCI-MS *m/z* 529 $(M+H)^+$.

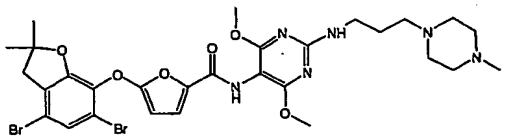
Example B86: 5-[(1-acetyl-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B86

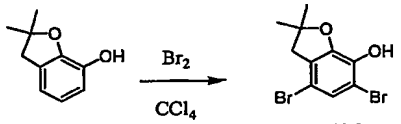
Compound B86 was synthesized in a manner analogous to that of B1, according to Scheme B, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.15 (s, 6H), 1.67 (t, 2H, J = 6.04 Hz), 2.17 (s, 3H), 3.66 (t, 2H, J = 6.14 Hz), 3.81 (s, 6H), 3.85 (s, 3H), 5.55 (d, 1H, J = 3.59 Hz), 7.15 (d, 1H, J = 3.40 Hz), 7.36 (s, 1H), 7.81(s, 1H), 9.16 (s, 1H), APCI-MS *m/z* 532 $(M+H)^+$.

Example B87: 5-[(4,6-dibromo-2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)oxy]-N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-2-furamide



B87

Compound B87 was synthesized according to Scheme B.

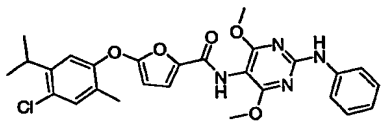


126

To a solution of phenol (3.28 g, 20 mmol) in carbon tetrachloride (50 mL) was added bromine (2.06 mL, 40 mmol) dropwise. The reaction mixture was stirred at r.t. overnight. It was washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate) and evaporated to a dark oil. The dibrominated product was purified by flash chromatography (eluting solvent: 1ethyl acetate/10 hexanes to 1ethyl acetate/5hexanes): 4.5 g (70%). NMR and mass spectrometry data consistent with the

title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.55 (6H, d), 1.90 (2H, sextet), 2.28 (3H, s), 2.46 - 2.51 (10H,m), 3.10 (2H, s), 3.44 (2H, m), 3.87 (6H, s), 5.52(1H, d, J = 3.78 Hz), 5.82 (1H, t), 6.93 (1H, s), 7.14 (1H, d, J = 3.78 Hz), 7.26 (1H, s), FI-PCI m/z 725.1 and 727.1 $(M+H)^+$.

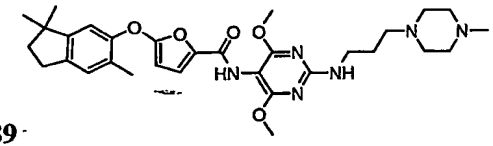
Example B88: N-(2-anilino-4,6-dimethoxypyrimidin-5-yl)-5-(4-chloro-5-isopropyl-2-methylphenoxy)-2-furamide



B88

Compound B88 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.19 (d, 6H, J = 6.80 Hz), 2.24 (s, 3H), 3.33 (dd, 1H, J = 7.18, 6.42 Hz), 3.98 (s, 6H), 5.35 (d, 1H, J = 3.78 Hz), 6.98 (s, 2H,) 7.04 (t, 1H, J = 7.55 Hz), 7.14 (d, 1H, J = 3.40 Hz), 7.32 (dd, 2H, J = 8.31, 7.55 Hz), 7.62 (d, 2H, J = 8.31 Hz), Mass $(M-H)^-$ = 521.3.

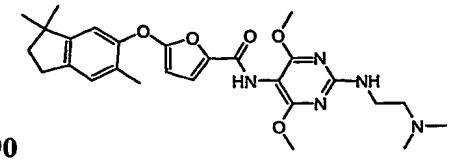
Example B89: N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-5-[(3.3.6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B89

Compound B89 was synthesized in manner analogous to that of B52. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.76 (dd, 2H, J = 12.84, 6.42 Hz), 1.92 (t, 2H, J = 7.18 Hz), 2.24 (s, 3H), 2.34 (s, 3H), 2.54 (dd, 10H, J = 7.18, 6.42 Hz), 2.84 (d, 2H, J = 7.18 Hz), 3.45 (dd, 2H, J = 12.09, 6.04 Hz), 3.87 (s, 6H), 5.29 (d, 1H, J = 6.80 Hz), 5.78 (bs, 1H), 6.82 (s, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.09 (m, 1H), APCI-MS m/z 579.7 $(M+H)^+$.

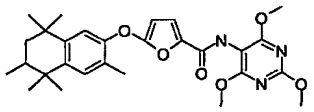
Example B90: N-(2-{[2-(dimethylamino)ethyl]amino}-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B90

Compound B90 was synthesized in manner analogous to that of B52. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.92 (dd, 2H, J = 14.73, 7.18 Hz), 2.23 (s, 3H), 2.28 (s, 6H), 2.51 (t, 2H, J = 6.04 Hz), 2.84 (dd, 2H, J = 14.35, 7.18 Hz), 3.48 (ddd, 2H, J = 11.71, 11.33, 5.67 Hz), 3.87 (s, 6H), 5.28 (m, 1H), 5.42 (t, 1H, J = 10.20 Hz), 6.82 (s, 1H), 6.97 (s, 1H), 7.05 (s, 1H), 7.10 (d, 1H, J = 3.40 Hz), APCI-MS m/z 579.7 $(M+H)^+$.

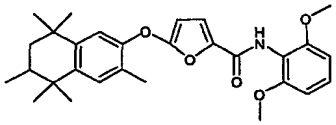
Example B91: 5-[(3,5,5,7,8,8-hexamethyl-5,6,7,8- tetrahydro-2-naphthalenyl]oxy}-N-(2,4,6-triethyl-5-pyrimidinyl)-2-furamide



B91

Compound B91 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, MeOH-d_4): δ 0.90 (d, 3H, J = 6.6 Hz), 0.96, 1.12, 1.14, 1.23 (4s, 3H each), 1.29 (dd, 1H, J = 2.4, 13.5 Hz), 1.55 (dd, 1H, J = 12.8, 13.4 Hz), 1.72-1.84 (m, 1H), 2.13 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 5.25 (d, 1H, J = 3.59 Hz), 6.91 (s, 1H), 7.05 (d, 1H, J = 3.59 Hz), 7.18 (s, 1H), 7.20-7.31 (m, 2H), APCI-MS *m/z* 510.4 $(M+H)^+$.

Example B92: N-(2,6-dimethoxyphenyl)-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl]oxy}-2-furamide

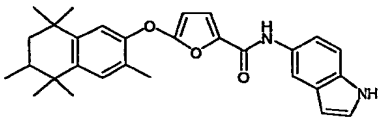


B92

Compound B92 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, MeOH-d_4): δ 0.99 (d, 3H, J = 6.8 Hz), 1.03, 1.22, 1.23, 1.32 (4s, 3H each), 1.38 (dd, 1H, J = 2.4,13.4 Hz), 1.64 (dd, 1H, J = 13.0, 13.2 Hz), 1.80-1.95 (m, 1H), 2.23 (s, 3H), 3.80 (s, 6H), 5.34 (d, 1H, J = 3.59 Hz), 6.68 (d, 1H, J = 8.3 Hz), 7.01 (s, 1H),

7.14 (d, 1H, J = 3.59 Hz), 7.22 (d, 1H, J = 8.5 Hz), 7.27 (s, 1H), APCI-MS *m/z* 478.2 $(M+H)^+$.

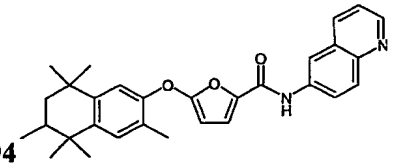
Example B93: 5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl]oxy}-N-(1H-indol-5-yl)-2-furamide



B93

Compound B93 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^1H (300 MHz, MeOH-d_4): δ 0.90 (d, 3H, J = 6.8 Hz), 0.96, 1.11, 1.13, 1.23 (4s, 3H each), 1.28 (dd, 1H, J = 2.6, 13.6 Hz), 1.54 (dd, 1H, J = 13.0, 13.2 Hz), 1.70-1.85 (m, 1H), 2.13 (s, 3H), 5.26 (d, 1H, J = 3.39 Hz), 6.32 (d, 1H, J = 3.59 Hz), 6.92 (s, 1H), 7.08 (s, 1H, J = 3.59 Hz), 7.12 (d, 1H, J = 3.0 Hz), 7.15-7.25 (m, 2H), 7.25-7.30 (m, 1H) 7.70-7.75 (m, 1H), APCI-MS *m/z* 457.4 $(M+H)^+$.

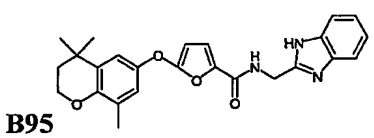
Example B94: 5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl]oxy}-N-(6-quinolinyl)-2-furamide



B94

Compound B94 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^1H (300 MHz, DMSO-d_6): δ 0.93 (d, 3H, J = 6.61 Hz), 1.00, 1.15, 1.18, 1.30 (4s, 3H each), 1.32 (dd, 1H, J = 2.2, 13.6 Hz), 1.54 (dd, 1H, J = 13.0, 13.2 Hz), 1.72-1.85 (m, 1H), 2.19 (s, 3H), 5.53 (d, 1H, J = 3.59 Hz), 7.05 (s, 1H), 7.32 (s, 1H), 7.38 (d, 1H, J = 3.58 Hz), 7.42-7.52 (m, 2H), 7.92-8.06 (m, 2H), 8.27 (d, 1H, J = 7.55 Hz), 8.43 (d, 1H, J = 1.8 Hz), 8.77 (dd, 1H, J = 1.7, 4.3 Hz), 10.32 (br s, 1H, NH), APCI-MS *m/z* 469.4 $(M+H)^+$.

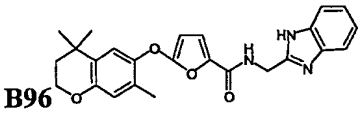
Example B95: N-(1H-benzimidazol-2-ylmethyl)-5-[(4,4,8-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B95

Compound B95 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, MeOH-d_4): δ 1.32 (s, 6H), 1.85 (dd, 2H, J = 5.29, 5.48 Hz), 2.15 (s, 3H), 4.22 (dd, 2H, J = 4.34, 5.28 Hz), 4.98 (s, 2H), 5.52 (d, 1H, J = 3.78 Hz), 6.79 (d, 1H, J = 2.2 Hz), 6.99 (d, 1H, J = 2.8 Hz), 7.21 (d, 1H, J = 3.59 Hz), 7.6-7.69 (m, 2H), 7.78 - 7.89(m, 2H), APCI-MS *m/z* 432.4 $(M+H)^+$.

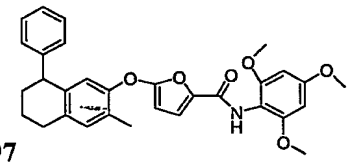
Example B96: N-(1H-benzimidazol-2-ylmethyl)-5-[(4,4,7-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B96

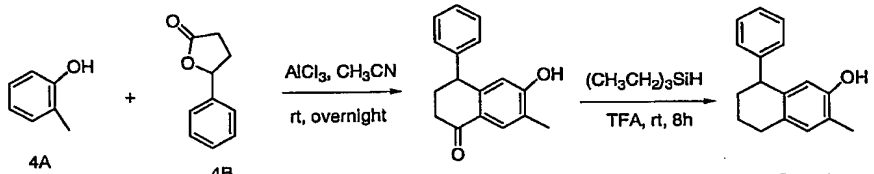
Compound B96 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, MeOH-d_4): δ 1.31 (s, 6H), 1.84 (dd, 2H, J = 5.29, 5.48 Hz), 2.16 (s, 3H), 4.18 (dd, 2H, J = 4.15, 5.29 Hz), 5.0 (s, 2H), 5.28 (d, 1H, J = 3.59 Hz), 6.69 (s, 1H), 7.08 (s, 1H), 7.19 (d, 1H, J = 3.59 Hz), 7.55 - 7.65 (m, 2H), 7.70-7.85(m, 2H), APCI-MS *m/z* 432.3 $(M+H)^+$.

Example 97: 5-[(3-methyl-8-phenyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B97

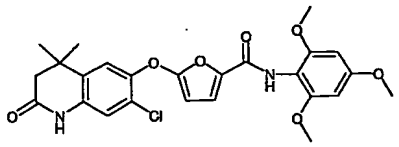
Compound B97 was synthesized according to Scheme B.



A solution of 4A (3g), 4B (4.5g) and $AlCl_3$ (5.6g) was stirred at room temperature overnight. The solution was extracted with EtOAc. Compound 4C (1.5g) was purified by column (hexane: EtOAC 2:1). To a solution of compound 4C (1.3g) in TFA (5 ml) was added $(CH_3CH_2)_3SiH$ at 0^{0}C. The solution was stirred for 2 hours. The solution was warmed up to room temperature and stirred overnight. The

solution was extracted with EtOAC, concentrated to give compound 4D (1.2g). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.55 - 1.75 (m, 3H), 1.92-2.05 (m, 1H), 2.03(s, 3H), 2.7-2.85 (m, 2H), 3.65 (s, 6H), 3.72 (s, 3H), 4.02 (t, 1H), 5.6 (d, 1H), 6.20 (s, 2H), 6.6 (s, 1H), 6.8 (s, 1H), 7.02 (d, 2H), 7.1 - 7.2 (m, 2H), 7.25-7.3 (t, 2H), 8.85 (s, 1H), APCI-MS *m/z* 514.3 $(M+H)^+$.

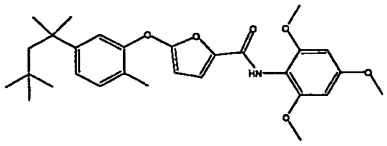
Example B98: 5-[(7-chloro-4,4-trimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B98

Compound B98 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO): δ 1.21 (s, 6H), 2.38 (s, 2H), 3.71 (s, 6H), 3.78 (s, 3H), 5.52 (d, 1H), 6.26 (s, 2H), 7.05 (s, 1H), 7.18 (d, 1H), 7.35 (s, 1H), 8.92 (s, 1H), 10.31 (s, 1H), APCI-MS *m/z* 501.2 $(M+H)^+$.

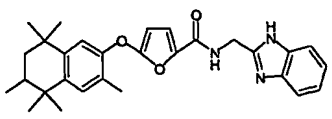
Example B99: 5-[2,4-dimethyl-5-(1,1,3,3-tetramethylbutyl)phenoxy]-N-(2,4,6-trimethoxylphenyl)-2-furamide



B99

Compound B99 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 0.97 (s, 9H), 1.64 (s, 6H), 2.15 (s, 2H), 2.35 (s, 3H), 2.56 (s, 3H), 4.05 (s, 6H), 4.06 (s. 3H), 5.32 (d, J = 6 Hz, 1H), 6.51 (s, 2H), 7.22 (s, 1H), 7.36 - 7 .40 (br, 2H), LC/MS $(M+H)^+$: 510.

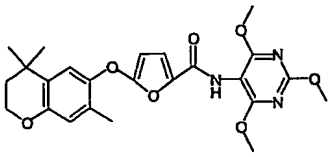
Example B100: N-(1H-benzimidazol-2-ylmethyl)-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl]oxy}-2-furamide



B100

Compound B100 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 0.99 (d, 3H, J = 6.8 Hz), 1.06, 1.18, 1.20, 1.33 (4s, 3H each), 1.30 - 1.45 (m, 1H), 1.62 (dd, 1H, J = 12.8, 13.4 Hz), 1.75 - 1.95 (m, 1H), 2.20 (s, 3H), 5.25-5.32 (m, 1H, NH), 5.32 (d, 1H, J = 3.58 Hz), 6.97 (s, 1H), 7.20 (s, 1H), 7.41 - 7.5 (m, 3H), 7.80 - 7.90 (m, 2H), 10.05 (br s, 1H, NH), APCI-MS *m/z* 472.3 $(M+H)^+$.

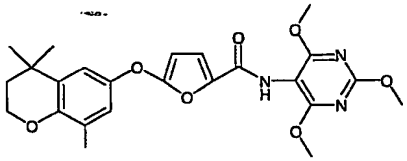
Example B101: N-(2,4,6-trimethoxy-5-pyrimidinyl)-5-[(4,4,7-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B101

Compound B101 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, MeOH-d_4): δ 1.29 (s, 6H), 1.80 (dd, 2H, J = 5.2, 5.4 Hz), 2.15 (s, 3H), 3.95 (s, 6H), 3.97 (s, 3H), 4.15 (dd, 2H, J = 5.2, 5.4 Hz), 5.22 (d, 1H, J = 3.59 Hz), 6.65 (s, 1H), 7.07 (s, 1H), 7.12 (d, 1H, J = 3.59 Hz), APCI-MS *m/z* 470.1 $(M+H)^+$.

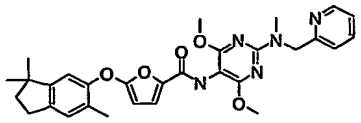
Example B102: N-(2,4,6-trimethoxy-5-pyrimidinyl)-5-[(4,4,8-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B102

Compound B102 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 1.31 (s, 6H), 1.82 (dd, 2H, J = 5.2, 5.4 Hz), 2.16 (s, 3H), 3.97 (s, 9H), 4.20 (d, 2H, J = 5.0, 5.4 Hz), 5.39 (d, 1H, J = 3.59 Hz), 6.74 (d, 1H, J = 3.0 Hz), 6.90 (d, 1H, J = 3.0 Hz), 6.99 (s, 1H), 7.12 (d, 1H, J = 3.59 Hz), APCI-MS *m/z* 470.2 $(M+H)^+$.

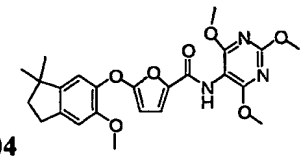
Example B103: N-{4,6-dimethoxy-2-[methyl(pyridin-2-ylmethyl)amino]pyrimidin-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B103

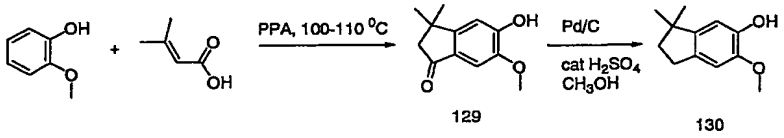
Compound B103 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

Example B104: 5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(2,4,6-trimethoxy-5-pyrimidinyl)-2-furamide



B104

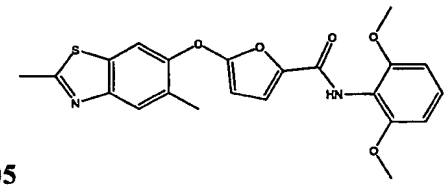
Compound B104 was synthesized according to Scheme B.



129 130

NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR (d_4-CH_3OH): δ 1.15 (s, 6H), 1.87 (t, 2H), 2.81 (t, 2H), 3.71 (s, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 5.14 (d, 1H), 6.89 (s, 2H), 7.02 (d, 1H), APCI-MS *m/z* 470.2 $(M+H)^+$.

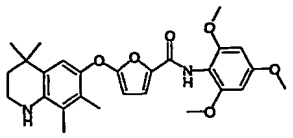
Example B105: 5-[(2,5-dimethyl-1,3-benzothiazol-6-yl)oxy]-N-(2,6-dimethoxyphenyl)-2-furamide



B105

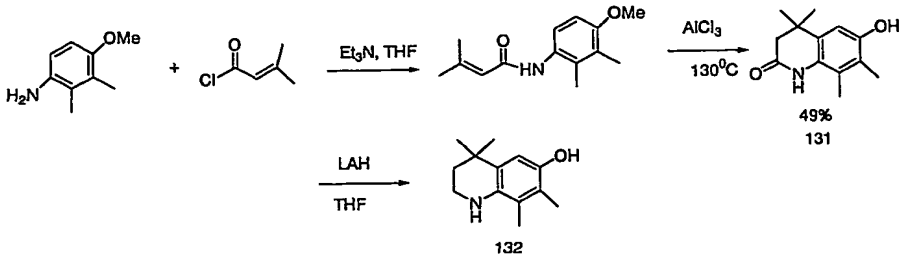
Compound B105 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR (DMSO-d6): δ 2.38 (s, 3H), 2.76 (s, 3H), 3.72 (s, 6H), 5.71 (d, J = 6 Hz, 1H), 6.69(d, J = 9 Hz, 2H), 7.21 - 7.26 (m, 2H), 7.86 (s, 1H), 8.87 (s, 1H), 9.10 (s, 1H), LC/ MS $(M+H)^+$: 425.

Example B106: 5-[(4,4,7,8-tetra-mehtyl-1,2,3,4-tetrahydroquinolin-6yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



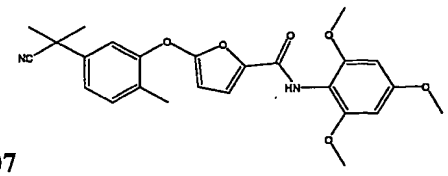
B106

Compound B106 was synthesized according to Scheme B.



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.20 (s, 6H), 1.61 (t, J = 6 Hz, 2H), 1.97 (s, 3H), 2.06 (s, 3H), 3.25 (br. 2H), 3.72 (s, 6H), 3.79 (s, 3H), 5.14 (d, J = 3 Hz, 1H), 6.27 (s, 2H), 6.89 (s, 1H), 7.10 (d, J = 3 Hz, 1H), 8.81 (s, 1H), LC/ MS $(M+H)^+$: 481.

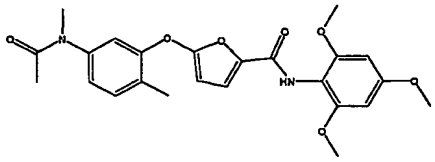
Example B107: 5-[5-(1-cyano-1-methylethyl)-2-methylphenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B107

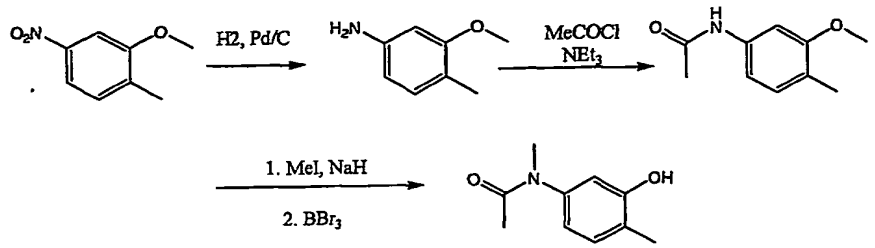
Compound B107 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.58 (s, 6H), 2.18 (s, 3H), 3.63 (s, 6H), 3.70 (s, 3H), 5.53 (d, J = 3 Hz, 1H), 6.18 (s, 2H), 7.11 (br. 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.26 (dd, J = 1.8 Hz, J = 9 Hz, 1H), 7.34 (d, J = 9 Hz, 1H), 8.84 (s, 1H), LC/ MS $(M+H)^+$: 451.

Example B108: 4-{5-[acetyl(methyl)amino]2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



B108

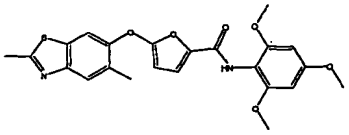
Compound B108 was synthesized according to Scheme B.



133

NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 1.87 (s, 3H), 2.36 (s, 3H), 3.22 (s, 3H), 3.81 (s, 6H), 5.62 (d, J = 3.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 7.08-7.13 (br. d, 2H), 7.18(d, J = 3.3 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), LC/MS $(M+H)^+$: 425.

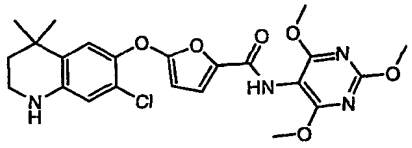
Example B109: 5-[(2,5-dimethyl-1,3-benzothiazol-6-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B109

Compound B109 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 2.38 (s, 3H), 2.76 (s, 3H), 3.71 (s, 6H), 3.78 (s, 3H), 5.70 (d, J = 3.3 Hz, 1H), 6.26 (s, 2H), 7.22 (d, J = 3.3 Hz, 1H), 7.85 (s, 1H), 7.87 (s, 1H), 8.96 (s, 1H), LC/ MS $(M+H)^+$: 455.

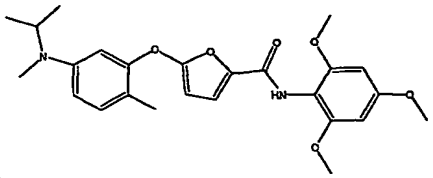
Example B110: 4-[(7-chloro-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]-N-(2,4,6-trimethoxypyrimidin-5-yl)-2-furamide



B110

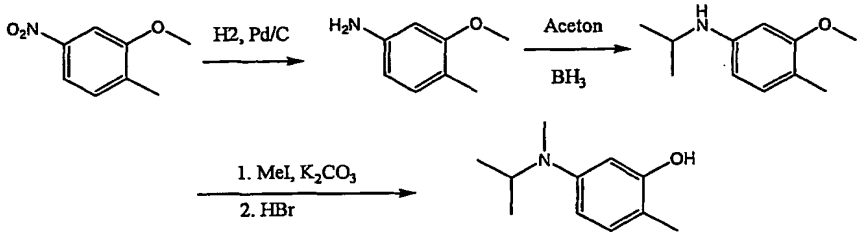
Compound B110 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (CD_3CN): δ 1.24 (s, 6H), 1.67 (t, 2H,), 3.2 (t, 2H), 3.92 (s, 6H), 3.96 (s, 3H), 4.81 (s, 1H), 5.28 (d, 1H), 6.59 (s, 1H), 7.03 (d, 1H), 7.186 (s, 1H), 7.57 (s, 1H), APCI-MS *m/z* 489.2 $(M+H)^+$.

Example B111: 5-{5-[isopropyl(methyl)amino]-2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



B111

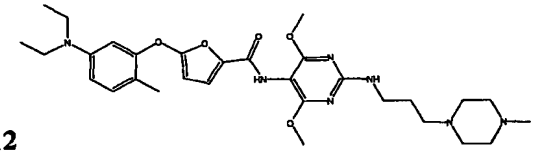
Compound B111 was synthesized according to Scheme B.



134

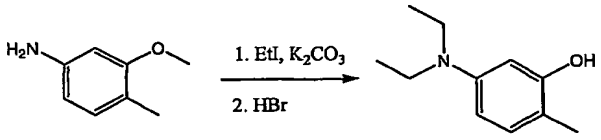
NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR (MeOD): δ 1.28 (s, 3H), 1.30 (s, 3H), 2.38 (s, 3H), 3.17 (s, 3H), 3.81 (s, 6H), 3.84 (s, 3H), 3.9-4.0 (m, 1H), 5.75 (d, J = 3.4 Hz, 1H), 6.29 (s, 2H), 7.11-7.30 (m, 3H), 7.49 (d, J = 9 Hz, 1H), LC/ MS $(M+H)^+$: 455.

Example B112: 5-{5-(diethylamino)-2-methylphenoxy]-N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)-propyl]amino} pyrimidin-5-yl)-2-furamide



B112

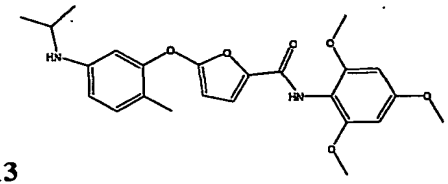
Compound B112 was synthesized according to Scheme B.



135

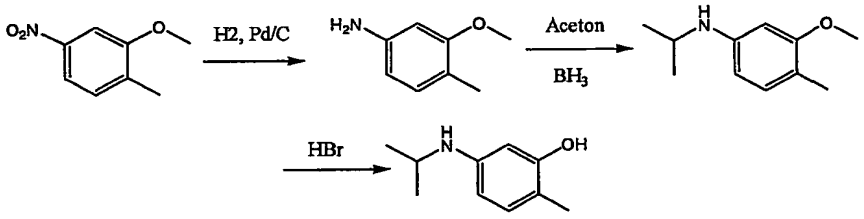
NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR (MeOD): δ 1.10 (dd, J = 7.18, 6.80 Hz, 6H), 1.86 (m, 2H), 2.13 (s, 3H), 2.53 (s, 3H), 2.58 - 2.95 (m, 10H), 3.45 (dd, J = 6.80, 6.42 Hz, 2H), 3.88 (s, 6H), 5.37 (d, J = 3.78 Hz, 1H), 6.40 (d, J = 2.27 Hz, 1H), 6.53 (dd, J = 8.31, 2.27 Hz, 1H), 7.06 (d, J = 8.31 Hz, 1H), 7.13 (d, J = 3.40 Hz, 1H), LC/ MS $(M+H)^+$: 582.

Example B113: 5-[5-(isopropylamino)-2-methylphenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



B113

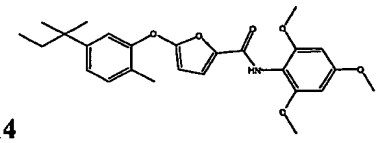
Compound B113 was synthesized according to Scheme B.



136

NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 1.49 (d, J = 9 Hz, 6H), 2.55 (s, 3H), 3.90 (m, 1H), 4.01 (s, 6H), 4.04 (s, 3H), 5.94 (d, J = 3 Hz, 1H), 6.49 (s, 2H), 7.14 (s, 1H), 7.22 (d, J = 6 Hz, 1H), 7.42 (s, 1H), 7.62 (d, J = 6 Hz, 1H), LC/ MS $(M+H)^+$: 441.

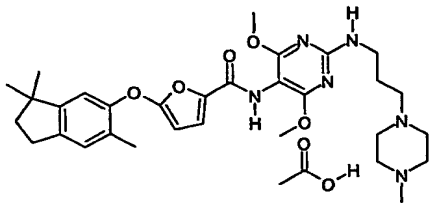
Example B114: 5-(2-methyl-5-tert-pentylphenoxy)-N-(2,4,6-trimethoxylphenyl)-2-furamide



B114

Compound B114 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 0.67 (t, J = 9 Hz, 3H), 1.25 (s, 6H), 1.63 (q, J = 9 Hz, 2H), 2.25 (s, 3H), 3.79 (3, 6H), 3.81 (s, 3H), 5.32 (d, J = 3 Hz, 1H), 6.26 (s, 6H), 7.06 (s, 1H), 7.12-7.17 (br.d, 2H), 7.23 (d, J = 9 Hz, 1H), LC/ MS $(M+H)^+$: 454.

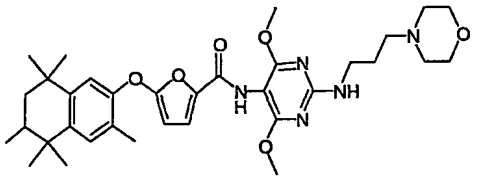
Example B115: N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide acetic acid salt



B115

Compound B115 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

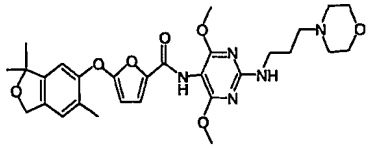
Example B116: N-(4,6-dimethoxy-2-{[3-(4-moprpholinyl)propyl]amino}-5-pyrimidinyl)-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B116

Compound B116 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 0.99 (d, 3H, J = 6.79 Hz), 1.05, 1.20, 1.24, 1.31 (4s, 3H each), 1.36 (dd, 1H, J = 2.2, 13.4 Hz), 1.62 (dd, 1H, J = 13.0, 13.2 Hz), 1.75-1.95 (m, 3H), 2.24 (s, 3H), 2.40-2.60 (m, 6H), 3.48 (dd, 2H, J = 6.0, 6.2 Hz), 3.70-3.81 (m, 4H), 3.87 (s, 6H), 5.32 (d, 1H, J = 3.59 Hz), 5.73 (t, 1H, J = 5.4, NH), 6.95 (s, 2H), 7.10 (d, 1H, J = 3.4 Hz), 7.19 (s, 1H), APCI-MS *m/z* 622.3 $(M+H)^+$.

Example B117: N-(4,6-dimethoxy-2-{[3-(4-morpholinyl)propyl]amino}-5-pyrimidinyl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide

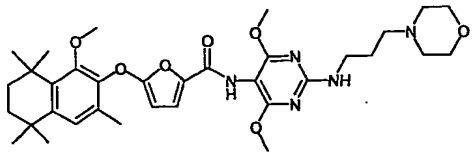


B117

Compound B117 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the desired product were as follows: ^{1}H (300 MHz, $CDCl_3$): δ 1.45 (s, 6H), 1.72-1.82 (m, 2H), 2.23 (s, 3H), 2.45-2.55 (m, 6H), 3.47 (dd, 2H, J = 6.0, 6.23 Hz), 3.74 (t, 4H, J = 4.54 Hz), 3.86 (s, 6H), 5.01 (s, 2H), 5.36 (d, 1H,

J = 3.59 Hz), 5.77(t, 1H, J = 5.48 Hz, NH), 6.79 (s, 1H), 6.90(d, 1H), 7.06 (s, 1H), 7.10 (d, 1H, J = 3.59 Hz), APCI-MS *m/z* 568.3 $(M+H)^+$.

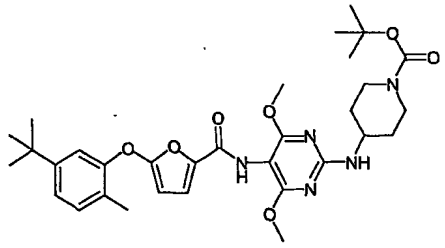
Example B118: N-(4,6-dimethoxy-2-{[3-(4-morpholinyl)propyl]amino}-5-pyrimidinyl)-5-[(1-methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-furamide



B118

Compound B118 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.26 (s, 6H), 1.35 (s, 6H), 1.60-1.67 (m, 4H), 2.12-2.16 (m, 2H), 2.19 (s, 3H), 2.85 - 2.94 (m, 2H), 3.16 - 3.21 (m, 2H), 3.49-3.57 (m, 4H), 3.86 (s, 3H), 3.94 (s, 6H), 3.98 - 4.01 (m, 4H), 5.10 (d, 1H, J = 3.78 Hz), 6.93 (s, 1H), 6.98 (s, 1H), 7.10 (d, 1H, J = 3.40 Hz), MS (APCI): 638.4 $(M+H)^+$.

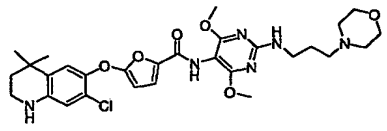
Example B119: 4-[(5-{[5-(5-tert-butyl-2-methylphenoxy)-2-furoyl]amino}-4,6-dimethoxypyrimidin-2-yl)amino]piperidine-1-carboxylate



B119

Compound B119 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the desired product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.29 (s, 9H), 1.45 (s, 9H), 1.95 (dd, 2H), 2.24 (s, 3H), 2.97 (t, 4H), 3.30 (s, 3H), 3.93 - 4.03 (m, 5H), 5.35 (d, 2H), 7.11 (s, 1H), 7.12 (d, 1H), 7.21 (dd, 2H), APCI-MS *m/z* 610.1 $(M+H)^+$.

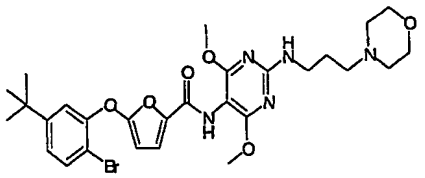
Example B120: 5-[(7-chloro-4,4-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-N-{2,6-dimethoxy-4-[3-(4-morpholinyl)propoxy]pyrimidinyl}-2-furamide



B120

Compound B120 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 6H), 1.61-1.9 (m, 4H), 2.45-2.49 (m, 6H), 3.30 (t, 2H), 3.47 (m, 2H), 3.74 (t, 4H), 3.87 (s, 6H), 5.21 (d, 1H), 5.72 (t, 1H), 6.49 (s, 1H), 6.96 (s, 1H), 7.03 (d, 1H), APCI-MS *m/z* 601.1 $(M+H)^+$.

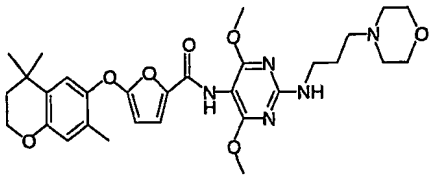
Example B121: 5-(2-bromo-5-tert-butylphenoxy)-N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-2-furamide



B121

Compound B121 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}HNMR (300 MHz, CD_3OD): δ 1.30 (s, 9H), 2.10 (m, 2H), 3.18 (m, 26H), 3.24 (m, 2H), 3.48 (m, 4H), 3.72 (m, 2H), 4.03 (s, 6H), 4.07 (m, 2H), 5.48 (d, 1H, J = 3 Hz), 7.15 (d, 3H, J = 3 Hz), 7.27 (m, 2H), 7.59 (d, 1H, J = 6 Hz).

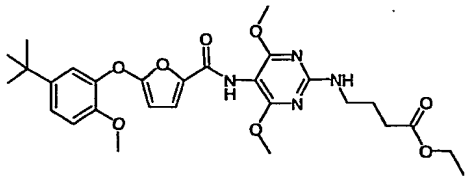
Example B122: N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-5-[(4,4,7-trimethyl-3,4-dihydro-2H-chromen-6-yl)oxy]-2-furamide



B122

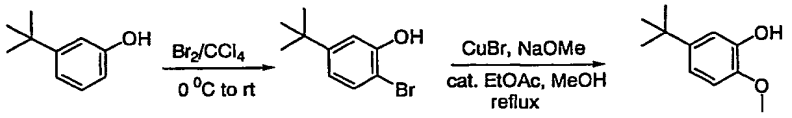
Compound B122 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H (300 MHz, DMSO-d_6): δ 1.22 (s, 6H), 1.73 (dd, 2H, J = 4.91, 5.28 Hz), 2.10 (s, 3H), 2.25 - 2.45 (m, 4H), 3.20 - 3.35 (m, 4H), 4.10 (t, 2H, J = 4.91 Hz), 5.30 (d, 1H, J = 3.4 Hz), 6.66 (s, 1H), 7.11 (d, 1H, J = 3.4 Hz), 7.13 (s, 1H), 8.82 (s, 1H, NH), APCI-MS *m/z* 582.3 $(M+H)^+$.

Example B123: ethyl 4-[(5-{[5-(5-tert-butyl-2-methoxyphenoxy)-2-furoyl]amino}-4,6-dimethoxy-2-pyrimidinyl)amino]butanoate



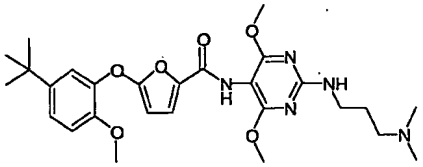
B123

Compound B123 was synthesized according to Scheme B, using HBTU as the coupling agent.



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H), 1.28 (s, 9H), 1.90 (quint, 2H), 2.45 (t, 2H), 3.40 (q, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 5.00 (t, 1H), 5.32 (d, 1H), 6.92 (d, 1H), 6.94 (d, 1H), 7.08 (d, 1H), 7.19(s, 1H), 7.21 (s, 1H), APCI-MS *m/z* 557.3 $(M+H)^+$.

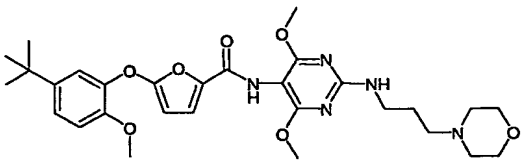
Example B124: 5-(5-tert-butyl-2-methoxyphenoxy)-N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxy-5-pyrimidinyl)-2-furamide



B124

Compound B124 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.20 (s, 9H), 1.70 (quint, 2H), 2.17 (s, 6H), 2.30 (t, 2H), 3.24 (t, 2H), 3.71 (s, 3H), 3.77 (s, 6H), 5.10 (d, 1H), 6.94 (d, 1H), 6.98 (d, 1H), 7.12 (s, 1H), 7.14 (d, 1H), APCI-MS *m/z* 528.3 $(M+H)^+$.

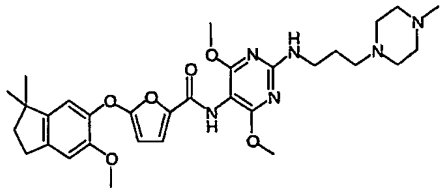
Example B125: [5-(tert-butyl)-2-methoxyphenoxy]-N-(4,6-dimethoxy]-2-{[3-(4-morpholinyl)propyl]amino}-5-pyrimidinyl)-2-furamide



B125

Compound B125 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.48 (s, 9H), 2.02 (t, 2H), 2.67 (m, 6H), 3.49 (t, 2H), 3.89 (t, 4H), 4.00 (s, 3H), 4.06 (s, 6H), 5.45 (d, 1H), 7.20 (d, 1H), 7.24 (d, 1H), 7.12 (s, 1H), 7.46 (s, 1H), 7.48 (s, 1H), APCI-MS *m/z* 570.3 $(M+H)^+$.

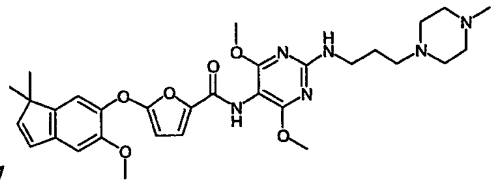
Example B126: N-(4,6-dimethoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy-2-furamide



B126

Compound B126 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.21 (s, 6H), 1.76 (quintet, 2H), 1.94 (t, 2H), 2.30 (s, 3H), 2.47 - 2.54 (m, 10H), 2.87 (t, 2H), 3.43 (m, 2H), 3.81 (s, 3H), 3.86 (s, 6H), 5.26 (d, 1H), 5.72 (br s, 1H), 6.84 (s, 1H), 6.90 (s, 1H), 6.96 (s, 1H), 7.08 (d, 1H), APCI-MS *m/z* 595.3 $(M+H)^+$.

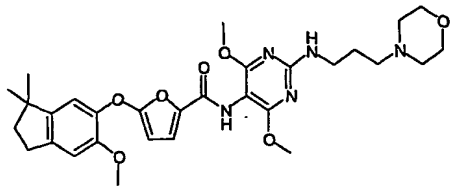
Example B127: N-(4,6-dimethoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl-5-[(5-methoxy-1,1-dimethyl-1H-inden-6-yl)oxy]-2-furamide



B127

Compound B127 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 6H), 1.92 (quintet, 2H), 2.34 (s, 3H), 2.52 - 2.59 (m, 6H), 2.87 (t, 2H), 3.87 (s, 3H), 3.88 (s, 6H), 5.30 (d, 1H), 5.70 (br s, 1H), 6.43 (s, 1H), 6.57 (d, 1H), 6.97 (s, 1H), 7.11 (d, 1H), 7.11 (s, 1H), APCI-MS *m/z* 593.3 $(M+H)^+$.

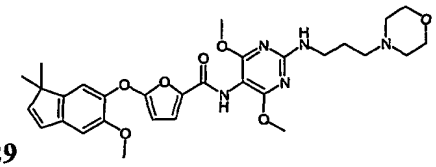
Example B128: N-(4,6-dimethoxy-2-{[3-(4-morpholinyl)propyl]amino}-5-pyrimidinyl)-5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B128

Compound B128 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 6H), 1.95 (quintet, 2H), 1.98 (t, 2H), 2.51 (m, 6H), 2.88 (t, 2H), 3.40 (t, 2H), 3.74 (t, 4H), 3.83 (s, 3H), 3.88 (s, 6H), 5.28 (d, 1H), 5.72 (br s, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 6.98 (s, 1H), 7.10 (d, 1H), APCI-MS *m/z* 582.3 $(M+H)^+$.

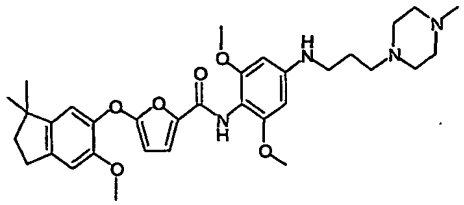
Example B129: N-(4,6-dimethoxy-2-{[3-(4-morpholinyl)propyl]amino}-5-pyrimidinyl)-5-[(5-methoxy-1,1-dimethyl-1H-inden-6-yl)oxy]-2-furamide



B129

Compound B129 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 6H), 1.86 (quintet, 2H), 2.53 (m, 6H), 2.88 (t, 2H), 3.40 (t, 2H), 3.78 (t, 4H), 3.87 (s, 3H), 3.88 (s, 6H), 5.30 (d, 1H), 5.74 (br s, 1H), 6.43 (d, 1H), 6.57 (d, 1H), 6.97 (s, 1H), 6.97 (s, 1H) 7.11 (d, 1H), 7.11 (d, 1H), APCI-MS *m/z* 580.3 $(M+H)^+$.

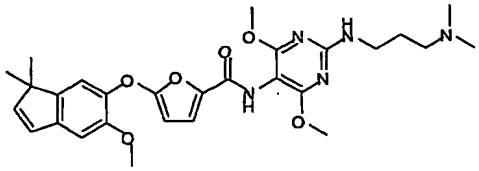
Example B130: N-(2,6-dimethoxy-4-{[3-(4-methyl-1-piperazinyl)propyl]amino}phenyl)-5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B130

Compound B130 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 6H), 1.81 (quintet, 2H), 1.96 (t, 2H), 2.52 (m, 10H), 2.88 (t, 2H), 3.19 (t, 2H), 3.78 (s, 6H), 3.78 (s, 3H), 3.83 (s, 6H), 5.29 (d, 1H), 5.84 (s, 2H), 6.85 (s, 1H), 6.92 (s, 1H), 6.92 (s, 1H), 7.04 (d, 1H), 7.12 (d, 1H), APCI-MS *m/z* 593.3 $(M+H)^+$.

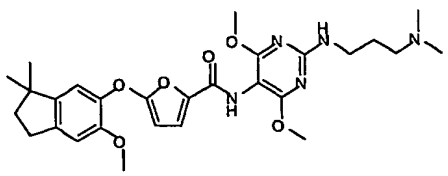
Example B131: N-(2-{[3-dimethylamino)propyl]amino}-4,6-dimethoxy-5-pyrimidinyl)-5-[(5-methoxy-1,1-dimethyl-1H-inden-6-yl)oxy]-2-furamide



B131

Compound B131 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 6H), 1.96 (quintet, 2H), 2.51 (s, 6H), 2.88 (t, 2H), 3.40 (t, 2H), 3.87 (s, 3H), 3.88 (s, 6H), 5.30 (d, 1H), 5.40 (br s, 1H), 6.43 (d, 1H), 6.57 (d, 1H), 6.97 (s, 1H), 6.99 (s, 1H), 7.11 (d, 1H), 7.11 (s, 1H), APCI-MS *m/z* 538.2 $(M+H)^+$.

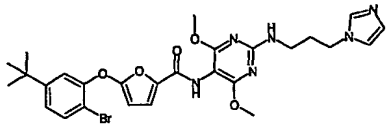
Example B132: N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxy-5-pyrimidinyl)-5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B132

Compound B132 was synthesized according to Scheme B, using HBTU as the coupling agent. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 6H), 1.82 (quintet, 2H), 1.95 (t, 2H), 2.36 (s, 6H), 2.48 (t, 2H), 2.88 (t, 2H), 3.44 (t, 2H), 3.83 (s, 3H), 3.88 (s, 6H), 5.27 (d, 1H), 5.31 (br s, 1H), 6.85 (s, 1H), 6.91 (s, 1H), 6.98 (s, 1H), 7.11 (d, 1H), APCI-MS *m/z* 540.3 $(M+H)^+$.

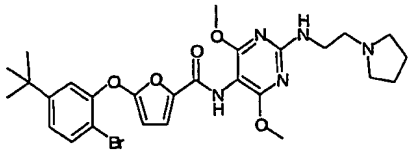
Example B133: 5-(2-bromo-5-tert-butylphenoxy)-N-(2-{[3-(1H-imidazol-1-yl)propyl]amino}-4.6-dimethoxypyrimidin-5-yl)-2-furamide



B133

Compound B133 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 2.12 (m, 2H), 3.43 (m, 2H), 3.86 (s, 6H), 4.10 (m, 2H), 4.98 (m, 1H), 5.45 (d, 1H, J = 3 Hz), 6.97 (s, 1H), 7.15 (m, 3H), 7.55(d, 2H, J = 9 Hz), 7.71 (s, 1H), APCI $(M+H)^+$: 599.

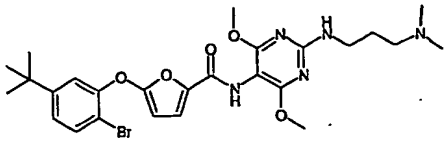
Example B134: 5-(2-bromo-5-tertbutylphenoxy)-N-{4,6-dimethoxy-2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}-2-furamide



B134

Compound B134 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 1.90 (m, 4H), 2.85 (m, 4H), 3.64 (m, 2H), 3.87 (s, 6H), 5.45 (d, 1H, J = 3 Hz), 5.63 (m, 1H), 6.97 (s, 1H), 7,15 (m, 3H), 7.53(d, 1H, J = 9 Hz), APCI $(M+H)^+$: 588.

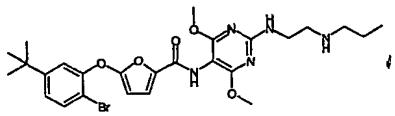
Example B135: 5-(2-bromo-5-tert-butylphenoxy)-N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxypyrimidin-5-yl)-2-furamide



B135

Compound B135 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.16(s, 3H), 1.26 (s, 3H), 1.31 (s, 3H), 2.12 (dd, 2H, J = 18.51, 7.18 Hz), 2.79 (s, 6H), 3.09 (dd, 2H, J = 7.18, 6.80 Hz), 3.56 (dd, 2H, J = 16.24, 6.04 Hz), 5.39 (s, 1H), 5.47 (d, 1H, J = 3.40 Hz), 6.97 (s, 1H), 7.11 (m, 1H), 7.13 (m, 1H), 7.18 (m, 1H), 7.55 (d, 1H, J = 8.31 Hz), APCI $(M+H)^+$: 577.

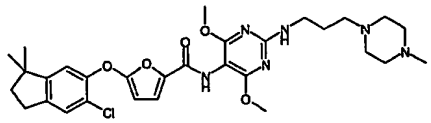
Example B136: 5-(2-bromo-5-tert-butylphenoxy)-N-(4,6-dimethoxy-2-{[2-(propylamino)ethyl]amino}pyrimidin-5-yl)-2-furamide



B136

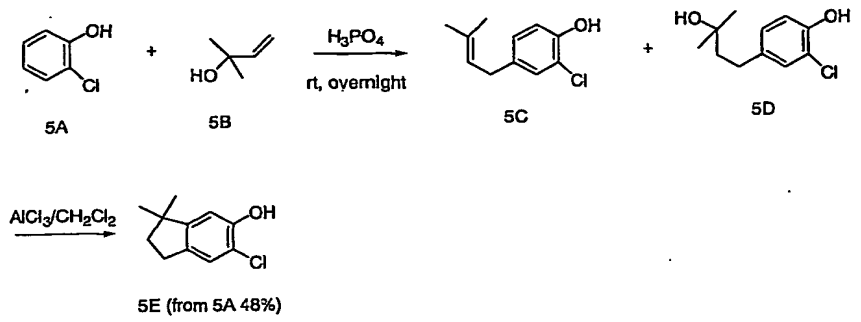
Compound B136 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.96 (dt, 3H, J = 7.66, 7.18 Hz), 1.29 (s, 9H), 1.66 (dd, 2H, J = 7.55, 7.18 Hz), 2.75 (d, 2H, J = 7.93 Hz), 3.02 (dd, 2H, J = 6.57, 5.29 Hz), 3.65 (m, 2H), 3.87 (s, 6H), 5.43 (d, 1H, J = 3.78 Hz), 5.75 (s, 1H), 6.98 (s, 1H), 7,12 (tt, 2H, J = 3.78, 3.40 Hz), 7.17(m, 1H), 7.53 (d, 1H, J = 8.31 Hz), APCI $(M+H)^+$: 577.

Example B137: 5-[(6-chloro-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(4,6-dimethoxy-2-{[3-(4-methyl-1-piperazinyl)propyl]amino}-5-pyrimidinyl)-2-furamide



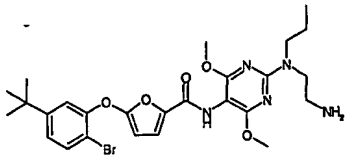
B137

Compound B137 was synthesized according to Scheme B.



Compound 5A (30g) was dissolved in H_2PO_3 (100 ml). To the solution was added compound 5B (26g). The mixture was stirred at room temperature overnight. The solution was extracted with EtOAC, washed with water, dried (Mg_2SO_4) and concentrated to give a crude mixture of 5C and 5D (50g). The mixture was dissolved in 300 ml of CH_2Cl_2 and $AlCl_3$ (31g) was added into. After being stirred at room temperature for 1.5 hour the solution was poured into ice water and extracted with EtOAC. Column chromatography (hexane:EtOAC 18:1) gave compound 5E (22g). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.19 (s, 6H), 1.89 (d, 2H, J = 7.18 Hz), 1.94 (d, 2H, J = 14.73 Hz), 2.82 (s, 3H), 2.86 -2.88 (m, 2H), 3.08-3.18 (m, 4H), 3.3-3.37 (m, 4H), 3.5 - 3.65 (m, 3H), 3.79 (s, 6H), 5.50 (d, 1H, J = 3.78 Hz), 7.18 (d, 1H, J = 3.40 Hz), 7.21 (s, 1H), 7.26-7.32 (m, 1H), 7.44 (s, 1H), 8.98 (s, 1H), MS (APCI): 599.3 $(M+H)^+$.

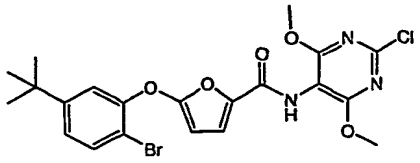
Example B138: N-{2-[(2-aminoethyl)(propyl)amino]-4,6-dimethoxypyrimidin-5-yl}-5-(2-bromo-5-tert-butylphenoxy)-2-furamide



B138

Compound B138 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.88 (dt, 3H, J = 7.66, 7.18 Hz), 1.28 (s, 9H), 1.66 (dd, 2H, J = 7.55, 7.18 Hz), 3.23 (m, 2H), 3.48 (m, 2H), 3.86 (m, 8H), 5.43 (d, 1H, J = 3 Hz), 7.15(m, 4H), 7.53 (d, 1H, J = 8.31 Hz), APCI $(M+H)^+$: 577.

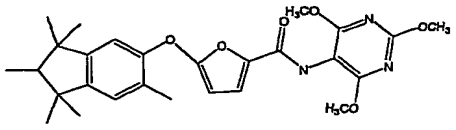
Example B139: 5-(2-bromo-5-tert-butylphenoxy)-N-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-2-furamide



B139

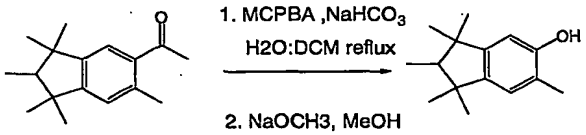
Compound B139 was synthesized according to Scheme B. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.29 (s, 9H), 3.99 (s, 6H), 4.01 (s, 6H), 5.43 (d, 1H, J = 3.40 Hz), 7.14 (dd, 3H, J = 3.78, 2.27 Hz), 7.15 (s, 3H), 7.53 (d, 1H, J = 8.31 Hz). APCI $(M+H)^+$: 510.

Example B140: *N*-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B140

Compound B140 was synthesized according to Scheme B. The overall yield was 21%.



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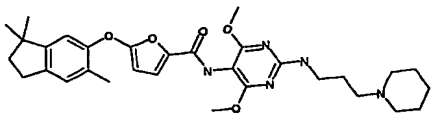
NMR data consistent with the title product were as follows: ^{1}H NMR, (DMSO): δ 0.94 (d, 3H, J = 7.37 Hz), 0.99 (s, 3H), 1.01(s, 3H), 1.19 (s, 3H), 1.23 (s, 3H), 1.79 (q, 1H, J = 7.37 Hz), 2.22 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 5.51 (d, 1H, J = 3.59 Hz), 6.97 (s, 1H), 7.14 (s, 1H), 7.20 (d, 1H, J = 3.59 Hz).

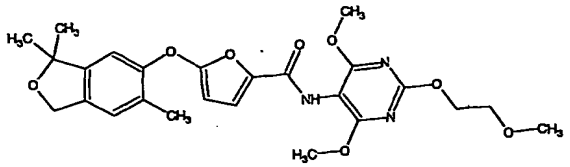
Example B141: N-{4,6-dimethoxy-2-[(3-piperidin-1-ylpropyl)amino]pyrimdine-5-yl}-5-[(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide



B141

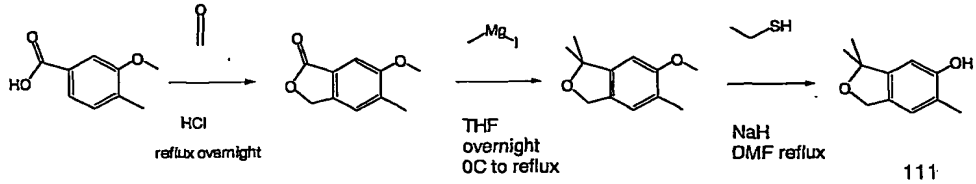
Compound B141 was synthesized according to scheme B.

Example B142: *N*-[4,6-dimethoxy-2-(2-methoxyethoxy)pyrimidin-5-yl]-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B142

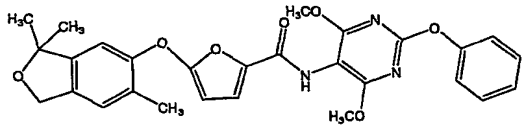
Compound B142 was synthesized according to Scheme B. The requisite phenol was prepared according to the following method:



111

NMR data consistent with the title product were as follows: ^{1}H NMR (MeOD): δ 1.40 (s, 6H), 2.24 (s, 3H), 3.36 (s, 3H), 3.70 (t, 2H, J = 4.53 Hz), 3.90 (s, 6H), 4.45 (dd, 2H, J = 4.91, 4.53 Hz), 4.95 (s, 2H), 5.38 (d, 1H, J = 3.40 Hz), 6.92 (s, 1H), 7.12 (m, 2H).

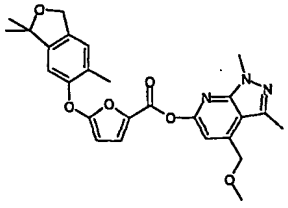
Example B143: *N*-(4,6-dimethoxy-2-phenoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B143

Compound B143 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR, (MeOD): δ 1.40 (s, 6H), 2.24 (s, 3H), 3.78 (s, 6H), 4.95 (s, 2H), 5.38 (d, 1H, J = 3.40 Hz), 6.92 (s, 1H), 7.16 (m, 5H), 7.37 (dd, 2H, J = 7.93, 7.55 Hz).

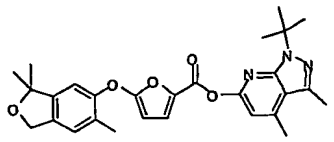
Example B144: 4-(Methoxymethyl)-1,3-dimethyl-1H-pyrazolo[3,4-*b*]pyridin-6-yl 5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furoate



B144

Compound B144 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR, (DMSO): δ 1.40 (s, 6H), 2.23 (s, 3H), 2.56 (s, 3H), 3.41 (s, 3H), 3.89 (s, 3H), 4.89 (s, 2H), 4.93 (s, 2H), 5.68 (d, 1H, J = 3.78 Hz), 6.99 (s, 1H), 7.21 (s, 1H), 7.24 (s, 1H), 7.65 (d, 1H, J = 3.78 Hz).

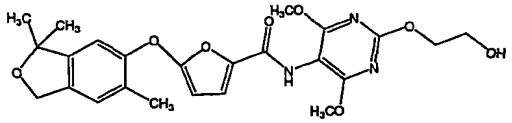
Example B145: 1-*tert*-butyl-3,4-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl 5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furoate



B145

Compound B145 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR, (DMSO): δ 1.39 (s, 6H), 1.67 (s, 9H), 2.23 (s, 3H), 2.59 (s, 3H), 2.66 (s, 3H), 4.93 (s, 2H), 5.67 (d, 1H, J = 3.78 Hz), 6.82 (s, 1H), 7.21 (s, 1H), 7.24 (s, 1H), 7.65 (d, 1H, J = 3.40 Hz).

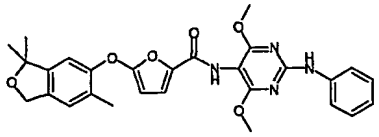
Example B146: N-[2-(2-hydroxyethoxy)-4,6-dimethoxypyrimidin-5-yl]-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B146

Compound B146 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR, (MeOD): δ 1.40 (s, 6H), 2.24 (s, 3H), 3.82 (dd, 2H, J = 5.29, 4.53 Hz), 4.39 (t, 2H, J = 4.91 Hz), 4.95 (s, 2H), 5.38 (d, 1H, J = 3.40 Hz), 6.92 (s, 1H), 7.11(m, 2H).

Example B147: *N*-(2-anilino-4,6-dimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide

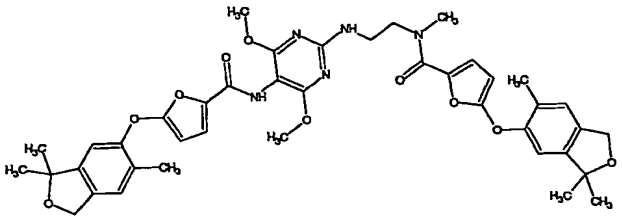


B147

Compound B147 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}H NMR, (DMSO): δ 1.37 (s, 6H), 2.23 (s, 3H), 3.87 (s, 6H), 4.90 (s, 2H), 5.54 (d, 1H, J = 3.40 Hz), 6.94 (dd, 1H, J =

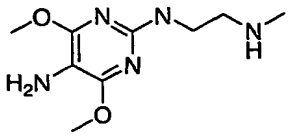
7.55, 7.18 Hz), 7.10 (s, 1H), 7.19 (d, 2H, J = 4.15 Hz), 7.27 (dd, 2H, J = 7.93, 7.55 Hz), 7.76 (d, 2H, J = 7.93 Hz).

Example B148: N-(4,6-dimethoxy-2-{[2-(methyl{5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furoyl}amino)ethyl]amino}pyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



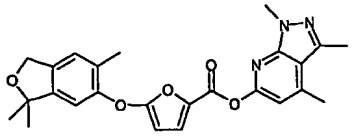
B148

Compound B148 was synthesized according to acyl chloride coupling method of Scheme B where the amine was:



and reacted at both the primary and alkyl-secondary amines to give the dimer B148. NMR data consistent with the title product were as follows: ^{1}H NMR, (MeOD): δ 1.35 (s, 6H), 1.39 (s, 6H), 2.19 (s, 3H), 2.23 (s, 3H), 3.14 (s, 3H), 3.55 (t, 2H, J = 6.04, 5.67 Hz), 3.78 (t, 2H, J = 6.80, 6.04 Hz), 3.83 (s, 6H), 4.91 (s, 2H), 4.94 (s, 2H), 5.33 (d, 1H, J = 3.40 Hz), 5.37 (d, 1H, J = 3.40 Hz), 6.82 (s, 1H), 6.90 (s, 1H), 6.96 (d, 1H, J = 3.40 Hz), 7.07 (d, 2H, J = 4.15 Hz), 7.11 (s, 1H).

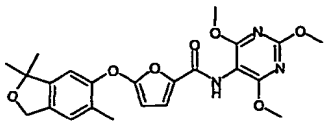
Example B149: 1,3,4-trimethyl-1H-pyrazolo[3,4-*b*]pyridin-6-yl 5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furoate



B149

Compound B149 was synthesized according to Scheme B. NMR data consistent with the title product were as follows: ^{1}HNMR, (MeOD): δ 1.40 (s, 6H), 2.22 (s, 3H), 2.59 (s, 3H), 2.66 (s, 3H), 3.87 (s, 3H), 4.95 (s, 2H), 5.44 (d, 1H, J = 3.78 Hz), 6.72 (s, 1H), 6.98 (s, 1H), 7.13 (s, 1H), 7.44 (d, 1H, J = 3.40 Hz).

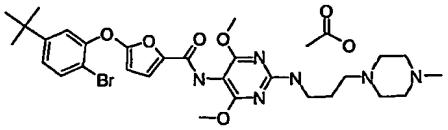
Example B150: *N*-(2,4,6-trimethoxypyrimidin-5-yl)-5-[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]-2-furamide



B150

Compound B150 was synthesized according to Scheme B. Yield of purified product was 36%. NMR data consistent with the title product were as follows: ^1H NMR ($CDCl_3$): δ 1.45 (s, 6H), 2.29 (s, 3H), 3.96 (s, 6H), 5.01 (s, 2H), 5.37 (d, 1H, J = 3.59 Hz), 6.80 (s, 1H), 7.07 (s, 1H), 7.14 (d, 1H, J = 3.59 Hz).

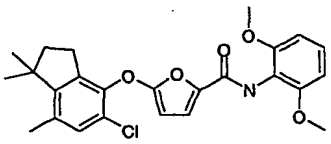
Example B151: 5-(2-bromo-5-tert-butylphenoxy)-N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-2-furamide acetate salt



B151

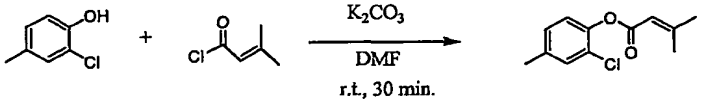
Compound B151 was synthesized according to scheme B.

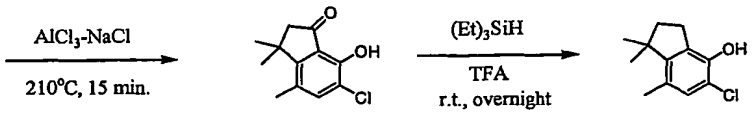
Example B152: 5-[(5-chloro-1,1,7-trimethyl-2,3-dihydro-1H-inden-4-yl)oxy]-N-(2,6-dimethoxyphenyl)-2-furamide



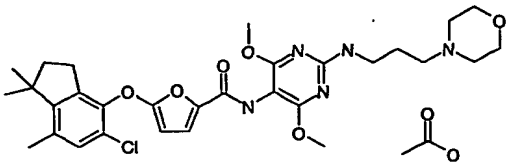
B152

Compound B152 was synthesized according to scheme B wherein the phenol was synthesized according to the following scheme.





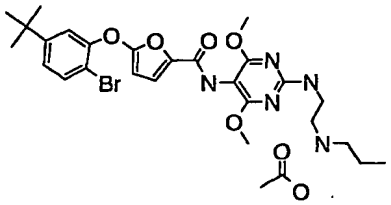
Example B153: 5-[(5-chloro-1,1,7-trimethyl-2,3-dihydro-1H-inden-4-yl)oxy]-N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-2-furamide acetate



B153

Compound B 153 was synthesized in a manner analogous to that of compound B152, according to scheme B.

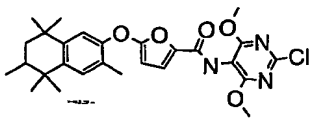
Example B154: 5-(2-bromo-5-tert-butylphenoxy)-N-(4,6-dimethoxy-2-{[2-(propylamino)ethyl]amino}pyrimidin-5-yl)-2-furamide acetate salt



B154

Compound B154 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

Example B155: N-(2-chloro-4,6-dimethoxypyrimidin-5-yl)-5-[(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furamide

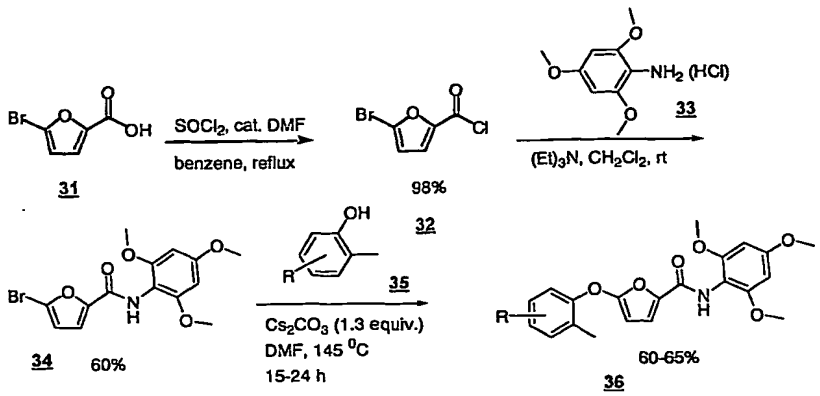


B155

Compound B155 was synthesized in a manner analogous to that of compound B1, according to scheme B, using similar starting materials and reaction conditions.

The following compounds were prepared according to Scheme C set forth below:

Scheme C



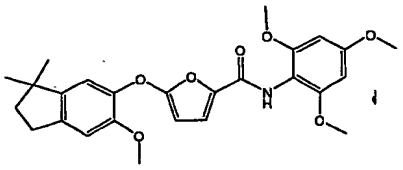
5-bromo-2-furoyl chloride 32: A suspension of 5-bromo-2-furoic acid (**31**, 57.3 g, 300 mmol) in anhydrous benzene (100 mL) containing few drops of anhydrous DMF was heated to reflux under nitrogen as thionyl chloride (1.1 equiv., 24.6 mL) in benzene (35 mL) was added dropwise. The resulting pale brown solution was further reflux for an additional 10 hours. The solution was cooled to room temperature and concentrated under vacuum to give 61.5 g (98%) of crude acid chloride. The ^{1}HNMR of the crude showed >95% purity. The crude acid chloride **32** thus obtained was used in the next step without further purification. NMR data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 6.74 (d, 1H), 7.38 (d, 1H).

5-bromo-N-(2,4,6-trimethoxyphenyl)-2-furamide 34: A mixture of trimethoxyaniline hydrochloride (**33**, 1.2 equiv., 21.1 g, 96 mmol) and triethyl amine (2.5 equiv., 27.9 mL, 200 mmol) in dichloromethane (200 mL) was stirred at 0°C under nitrogen as a solution of 5-bromo-2-furoyl chloride (16.8 g, 80 mmol) in dichloromethane (120 mL) was added dropwise. The solution was allowed to warm to room temperature and further stirred for 12 hours. The resulting suspension was washed several times with 2N hydrochloric acid, saturated sodium bicarbonate, brine and water successively. The organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum to give about 25 g of brown colored crude material. The crude material (in two equal batches) was subjected to silica gel chromatography using ethyl acetate/hexane 3:2 as the eluant to give 17.1 g (60%) of the desired bromofuranamide **34**. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 9H), 6.18 (s, 2H), 6.47 (d, 1H), 7.19 (d, 1H), 7.29 (br s, 1H).

5-aryloxy-2-furamide 36: A suspension of a phenol (**35**, 2.85 g, 13 mmol) and cesium carbonate (1.3 equiv., 4.24 g, 13 mmol) in anhydrous DMF (20 mL) was

stirred at room temperature under nitrogen for 15 minutes before adding 5-bromo-N-(2,4,6-trimethoxyphenyl)-2-furamide (**34**, 3.57 g, 10 mmol) at once. The resulting suspension was stirred at 145 °C (bath temperature) for 18 hours. The progress of the reaction was monitored by TLC and FIMS. The suspension was quenched with cold water and extracted several times with chloroform. The organic layer was washed with brine and water, dried (anhydrous sodium sulfate) and concentrated. The crude brown oil was further dried under high vacuum to remove last traces of solvents. The residue thus obtained was either recrystallized from ether or subjected to chromatography and dried overnight at 45 °C under vacuum to give title compound (60-65%) as a white solid which showed >95% purity by HPLC analysis.

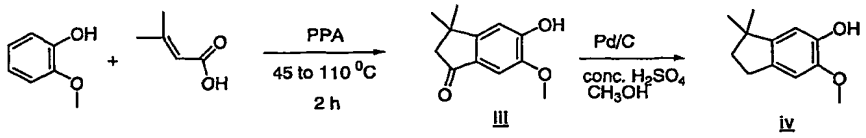
Example C1: 5-[(6-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C1

Compound C1 was synthesized according to Scheme C, using similar starting compounds and reaction conditions, with the exception that the residue obtained from the reaction between 5-bromo-N-(2,4,6-trimethoxyphenyl)-2-furamide and 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol was subjected to chromatography to give Compound C1 and dried overnight at 45 °C under vacuum to give title compound (60-65%) as a white solid, which showed >95% purity by HPLC analysis.

The requisite phenol, 6-methoxy-3,3-dimethyl-5-indanol, was prepared starting from 2-methoxyphenol via Fries rearrangement as described below:



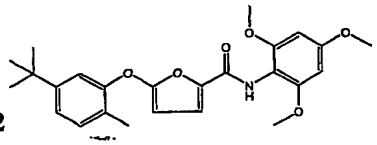
III iv

5-hydroxy-6-methoxy-3,3-dimethyl-1-indanone (iii): A mixture of 3,3-dimethylacrylic acid, 2-methoxyphenol (1.25 equiv.), and polyphosphoric acid (3 g/mmol) was heated to 45 ^{0}C for 0.5 hours. The reaction temperature was gradually increased to 110 ^{0}C and kept at that temperature for 2 hours. The viscous oil was cooled to 55-60 ^{0}C and extracted extensively with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude

residue was recrystallized from ether to afford 5-hydroxy-6-methoxy-3,3-dimethyl-1-indanone in 30-35% isolated yield. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 6H), 2.51 (s, 2H), 3.91 (s, 3H), 6.35 (s, 1H), 6.98 (s, 1H), 7.16 (s, 1H).

6-methoxy-3,3-dimethyl-5-indanol (iv): 5-hydroxy-6-methoxy-3,3-dimethyl-1-indanone was hydrogenated with 10% Pd on carbon (25 mg/mmol), in the presence of catalytic amount of concentrated H_2SO_4 (25 mg/mmol) in methanol (2 mL/mmol) for 15 hours. The resulting suspension was filtered through Celite and washed the precipitate with ethyl acetate. The filtrate was dried over Na_2SO_4 and concentrated to give 6-methoxy-3,3-dimethyl-5-indanol in 90% yield. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 6H), 1.78 (t, 2H), 2.70 (t, 2H), 3.74 (s, 3H), 5.41 (br s, 1H), 6.58 (s, 2H). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 6H), 2.36 (s, 3H), 3.85 (s, 9H), 4.25 (m, 1H), 5.44 (d, 1H), 5.91 (br d, 1H), 6.17 (s, 2H), 7.11 (d, 1H), 7.18 (s, 1H), 7.32 (d, 1H), 7.48 (d, 1H), 7.51 (s, 1H), MS (APCI +): 469.1 $(M+H)^+$.

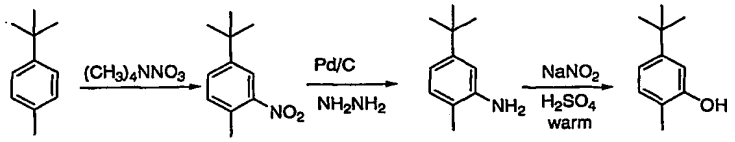
Example C2: 5-(5-tert-butyl-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



C2

Compound C2 was synthesized in a manner analogous to that of C1, according to Scheme C.

The requisite phenol for the synthesis of Compound C2, 5-tert-butyl-2-methyl-phenol, was prepared as follows:



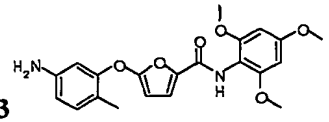
143

5-tert-butyl-2-nitro-toluene was synthesized from 4-tert-butyltoluene in 90% yield using tetramethylammonium nitrate according to the nitration procedure discussed in detail above. The regiochemistry of the nitration product was confirmed by NOE studies. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 9H), 2.42 (s, 3H), 7.12 (d, 1H), 7.40 (d, 1H), 7.84 (s, 1H).

The reduction of nitro compound to corresponding aniline was accomplished by hydrogenation with excess hydrazine (~50 equiv.) in the presence of Pd/C (10 mol %) in ethanol (2.5 mL/mmol) at room temperature for 15 hours. The aniline derivative was isolated as its HCl salt in 85-90% yield. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 9H), 2.00 (s, 3H), 6.50 (s, 1H), 6.56 (d, 1H), 6.82 (d, 1H).

5-tert-butyl-2-methylaniline was diazotized under standard conditions ($NaNO_2$, 1.1 equiv.; concentrated H_2SO_4 0.25 mL/mmol; H_2O, 1.7 mL/mmol, 0 ^{0}C) which upon heating at 50 ^{0}C for 2 hours afforded the requisite phenol in 30-35% yield. NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 2.43 (s, 3H), 4.82 (br s, 1H), 6.54 (d, 1H), 6.83 (s, 1H), 7.00 (d, 1H). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_6-DMSO): δ 1.23 (s, 9H), 2.20 (s, 3H), 3.70 (s, 3H), 3.77 (s, 6H), 5.50 (d, 1H), 6.25 (s, 2H), 7.11 (s, 1H), 7.32-7.50 (m, 3H), 8.88 (s, 1H). The overall yield was 15%, APCI-MS m/z 440.1 $(M+H)^+$.

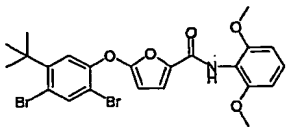
Example C3: 5-(5-amino-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



C3

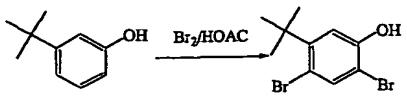
Compound C3 was synthesized in a manner analogous to that of C1, according to Scheme C. The overall yield was 60%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 2.16 (s, 3H), 3.78 (s, 3H), 3.82 (s, 6H), 5.46 (d, 1H), 6.28 (s, 2H), 6.50 (d, 1H), 6.52-6.56 (dd, 1H), 7.01 (d, 1H), 7.15 (d, 1H), APCI-MS m/z 399.2 $(M+H)^+$.

Example C4: 5-[2,4-dibromo-5(tert-butyl)phenoxy]-N-(2,6-dimethoxyphenyl)-2-furamide



C4

Compound C4 was synthesized in a manner analogous to that of C1, according to Scheme C. Compound C4 was obtained as white solid (23 mg, 6.5 %). The requisite phenol was prepared as follows:

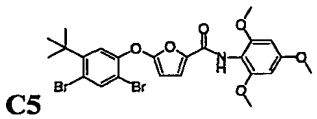


144

To a solution of 3-tert-butylphenol (1.5 g, 10 mmol) in HOAc (4 mL) was added Br_2 (2 mL, 15 mmol). The reaction mixture was stirred at room temperature over night. It was quenched with ascorbic acid. The crude product was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and taken to dryness. Column chromatography with EtOAc and hexane (1:10) offered white solid product (0.42 g, 14%). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 5.34 (1H, s), 7.11 (1H, s), 7.65 (1H, s), APCI-MS *m/z* 305 $(M-H)^-$.

5-bromo-N-(2,6-dimthyloxyphenyl)-2-furamide (0.2 g, 0.49 mmol) and cesium carbonate (0.21 g, 0.63 mmol) were added in the flask containing DMF (2 mL). The reaction mixture was gently heated at 130°C overnight. It was quenched with water, extracted with EtOAc and washed with water and brine. Organic layer was dried over Na_2SO_4 and taken to dryness. Crude product was purified by HPLC. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, DMSO): δ 1.48 (9H, s), 3.78 (6H, s), 5.86 (1H, d, J = 3 Hz), 6.75 (2H, d, J = 9 Hz), 7.26 – 7.28 (2H, m), 7.39 (1H, s), 8.07 (1H, s), 9.20 (1H, s), APCI-MS *m/z* 552 $(M+H)^+$.

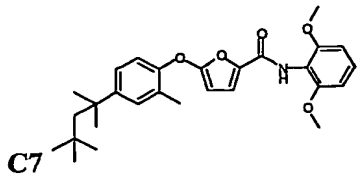
Example C5: 5-[2,4-dibromo-5(tert-butyl)phenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C5

Compound C5 was synthesized in a manner analogous to that of C1, according to Scheme C. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, DMSO): δ 1.48 (s, 9H), 3.76-3.84 (m, 9H), 5.84 (d, 1H, J = 3 Hz), 6.32 (s, 2H), 7.27 (brs, 1H), 7.38 (s, 1H), 8.07 (s, 1H), 9.03 (s, 1H), APCI-MS *m/z* 584 $(M+H)^+$.

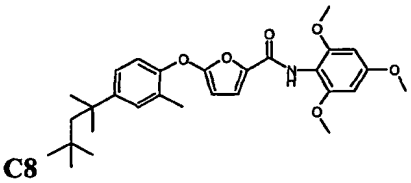
Example C7: N-(2,6-dimethoxyphenyl)-5-[2-methyl-4-(1,1,3,3-tetramethylbutyl)phenoxy]-2-furamide



C7

Compound C7 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 0.73 (9H, s), 1.36 (6H, s), 1.72 (2H, s), 2.30 (3H, s), 3.85 (6H, s), 5.27-5.28 (1H, d, J = 3.59 Hz), 6.59-6.62 (2H, d, J = 8.31 Hz), 6.97-7.00 (1H, d, J = 8.50 Hz), 7.14-7.15 (1H, d, J = 3.59 Hz), 7.18-7.21 (1H, d, J = 8.31 Hz), 7.19-7.21 (1H, d, J = 8.50 Hz), 7.24 (1H, s); m/z 466.

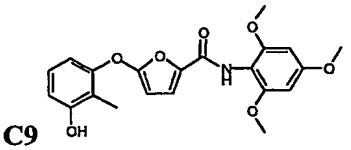
Example C8: 5-[2-Methyl-4-(1,1,3,3-tetramethylbutyl)phenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C8

Compound C8 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 0.72 (9H,s), 1.35 (6H, s), 1.71(2H, s), 2.28 (3H, s), 3.81(9H, s), 5.25-5.26 (1H, d, J = 3.59 Hz), 6.16 (2H, s), 6.96-6.99 (1H, d, J = 8.49 Hz), 7.13-7.14 (1H, d, J = 3.02 Hz), 7.18-7.21 (1H, d, J = 8.31 Hz), 7.23 (1H, s); m/z 496.

Example C9: 5-(3-hydroxy-2-mehtylphenoxy)-N-(2,4,6-trimethyoxyphenyl)-2-furamide

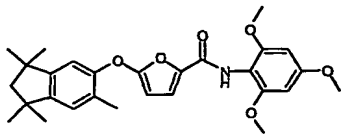


C9

Compound C9 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR, (MeOD): δ 2.14 (3H, s), 3.81 (6H, s), 3.82 (3H, s), 5.41-5.42

(1H, d, J = 3.59 Hz), 6.27 (2H, s), 6.58-6.61 (1H, d, J = 4.91 Hz), 6.67-6.69 (1H, d, J = 8.31 Hz), 7.01-7.06 (1H, t, J = 5.85 Hz), 7.13 (1H, d, J = 3.02 Hz); m/z 400.

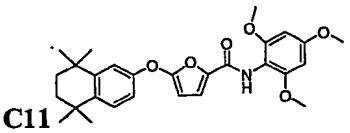
Example C10: 5-[(1,1,3,3,6-pentamethyl-2,3-dihydro-1H-inden-5-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C10

Compound C10 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. Yield of purified product was 4%. NMR data consistent with the title product were as follows: ^{1}H NMR, ($CDCl_3$): δ 1.27 (6H,s), 1.30 (6H, s), 1.92 (2H, s), 2.27 (3H, s), 3.81 (9H, s), 5.33-5.35 (1H, d, J = 3.40 Hz), 6.17 (2H, s), 6.18 (1H, s), 6.69 (1H, s), 7.15-7.16 (1H, d, J = 3.40 Hz); m/z 480.

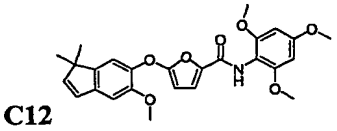
Example C11: 5-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C11

Compound C11 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. Yield of purified product was 4%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_6-DMSO): δ 1.30 (s, 12H), 1.70 (s, 4H), 3.78 (s, 6H), 3.85 (s, 3H), 5.85 (d, 1H), 6.33 (s, 2H), 6.95-6.99 (dd, 1H), 7.19 (d, 1H), 7.43 (d, 1H), 8.98 (s, 1H), APCI-MS *m/z* 480.1 $(M+H)^+$.

Example C12: 5-[(5-methoxy-1,1-dimethyl-1H-inden-6-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide

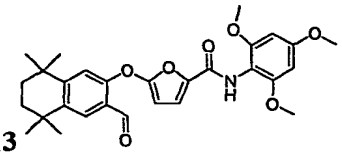


C12

Compound C12 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 1.28 (s, 6H), 3.80 (s, 3H), 3.81 (s, 3H), 3.84 (s, 6H), 5.24 (d,

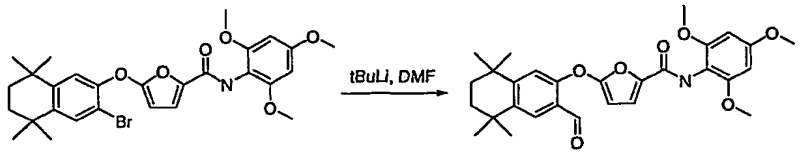
1H), 6.26 (s, 2H), 6.44 (d, 1H), 6.62 (d, 1H), 7.10 (d, 1H), 7.10 (s, 1H), 7.20 (s, 1H), APCI-MS *m/z* 466.2 $(M+H)^+$.

Example C13: 5-[(3-formyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



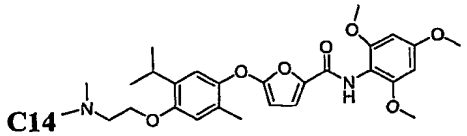
C13

Compound C13 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions.



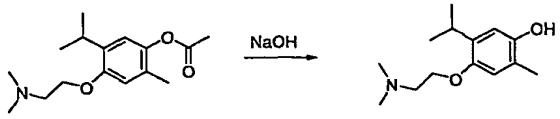
NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR ($CDCl_3$): δ 1.18 (s, 6H), 1.23 (s, 6H), 1.62 (s, 4H), 3.73 (s, 9H), 5.55 (d, 1H), 6.08 (s, 2H), 6.89 (d, 1H), 7.08 (d, 1H), 7.09 (s, 1H), 7.82 (s, 1H), 10.32 (s, 1H), APCI-MS *m/z* 508.2 $(M+H)^+$.

Example C14: 5-{4-[2-(dimethylamino)ethoxy]-5-isopropyl-2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



C14

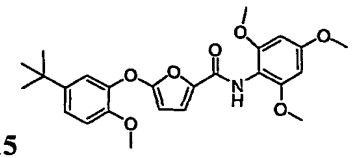
Compound C14 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions.



145

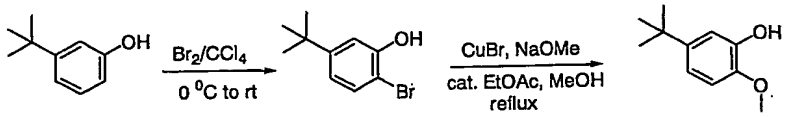
NMR and mass spectrometry data consistent with the title product were as follows: ^1H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.18 (s, 3H), 2.24 (s, 3H), 2.44 (s, 6H), 2.90 (t, 2H), 3.29-3.35 (s, m), 3.79 (s, 6H), 3.81 (s, 3H), 4.14 (t, 2H), 5.21 (d, 1H), 6.26 (s, 2H), 6.87 (s, 1H), 6.99 (s, 1H), 7.11 (d, 1H), APCI-MS *m/z* 513.4 $(M+H)^+$.

Example C15: 5-(3-tert-butyl-5-methoxyphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



C15

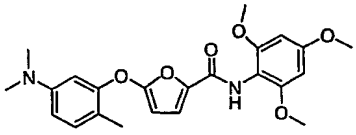
Compound C15 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions.



120 137

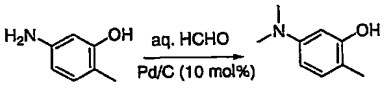
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_6-DMSO): δ 1.26 (s, 9H), 3.72 (s, 6H), 3.79 (s, 6H), 5.35 (d, 1H), 6.27 (s, 2H), 7.14 (d, 1H), 7.14 (d, 1H), 7.2 (d, 1H), 7.25 (s, 1H), 8.86 (s, 1H), APCI-MS *m/z* 456.1 $(M+H)^+$.

Example C16: 5-[5-(dimethylamino)-2-methylphenoxy]-N-(2,4,6-trimethoxyphenoxy)-2-furamide



C16

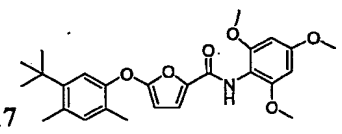
Compound C16 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions.



151

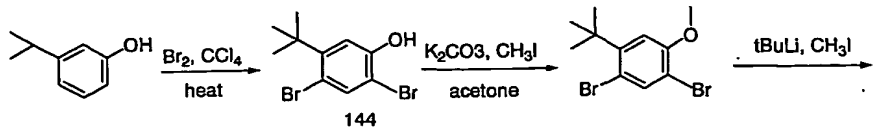
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (d_4-CH_3OH): δ 2.26 (s, 3H), 3.05 (s, 6H), 3.79 (s, 6H), 3.82 (s, 3H), 5.50 (d, 1H), 6.27 (s, 2H), 6.80 (d, 1H), 6.90 (d, 1H), 7.25 (s, 1H), 7.35 (d, 1H), APCI-MS *m/z* 427.2 $(M+H)^+$.

Example C17: 5-(5-tert-butyl-2,4-dimethylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

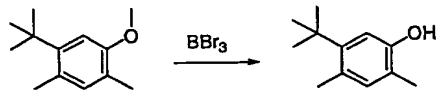


C17

Compound C17 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions.



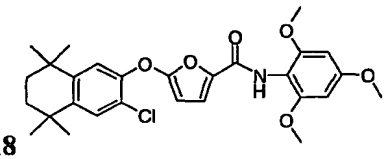
144



148

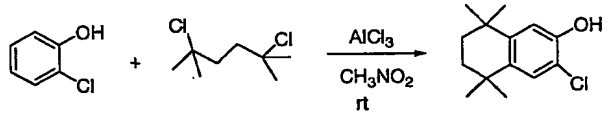
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H), 2.21 (s, 3H), 2.49 (s, 3H), 3.81 (s, 9H), 5.25 (d, 1H), 6.18 (s, 2H), 6.99 (s, 1H), 7.09 (d, 1H), 7.09 (s, 1H), 7.17 (s, 1H), APCI-MS *m/z* 454.3 $(M+H)^+$.

Example C18: 5-[(3-Chloro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



C18

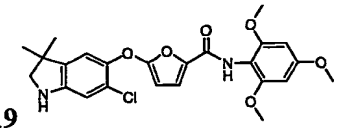
Compound C18 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following scheme:



38% yield

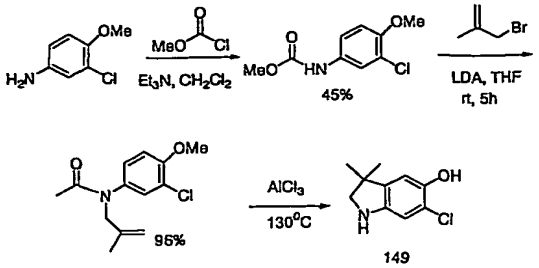
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (CDCl3): δ 1.22 (s, 6H), 1.27 (s, 6H), 1.67 (s, 4H), 3.81 (s, 9H), 5.43 (d, 1H), 6.17 (s, 2H), 7.11 (d, 1H), 7.18 (s, 1H), 7.34 (s, 1H), APCI-MS *m/z* 514.4 $(M+H)^+$.

Example C19: 5-[(6-chloro-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide(8783)



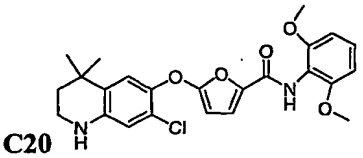
C19

Compound C19 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. The requisite phenol was synthesized according to the following scheme:



NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.23 (s, 6H), 2.60 (s, 1H) 3.33 (s, 2H), 3.39 (s, 2H), 3.75 (s, 9H), 5.27 (d, 1H, J = 3.59 Hz), 6.10 (s, 2H), 6.70 (s, 1H), 6.84(s, 1H), 7.06 (d, 1H, J = 3.40 Hz), 7.19 (s, 1H), 7.22 (s, 1H), APCI-MS *m/z* 473 $(M+H)^+$.

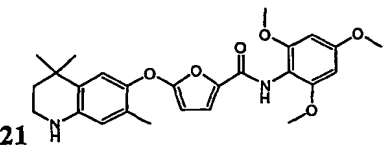
Example C20: 5-[(7-chloro-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]-N-(2,6-dimethoxyphenyl)-2-furamide



C20

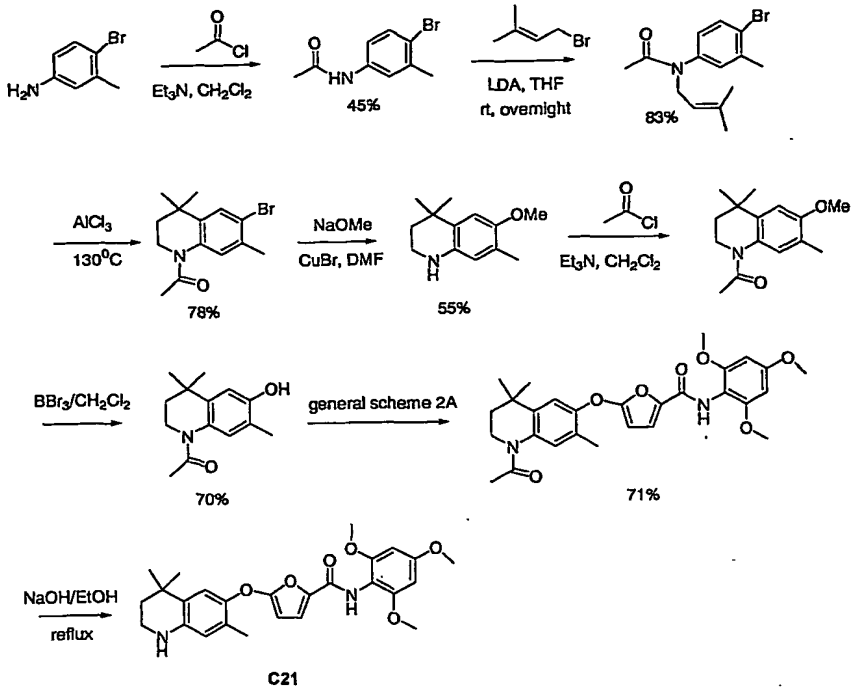
Compound C20 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d6): δ 1.11 (s, 6H), 1.53 (t, 2H, J = 5.67 Hz), 3.10 (t, 2H, J = 5.67 Hz), 3.68 (s, 6H), 5.23 (d, 1H, J = 3.59 Hz), 6.52 (s, 1H), 6.63 (m, 2H), 7.07 (d, 1H, J = 3.40 Hz) 7.12 (s, 1H), 7.19 (d, 1H, J = 4.15 Hz), 8.96 (s, 1H), APCI-MS *m/z* 456 $(M+H)^+$.

Example C21: N-(2,4,6-trimethoxyphenyl)-5-[(4,4,7-trimethyl-1,2,3,4-tetrahydro-6-quinolinyl)oxy]-2-furamide



C21

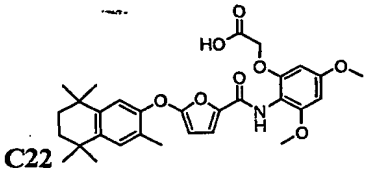
Compound C21 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. The particular procedure utilized is shown below:



C21

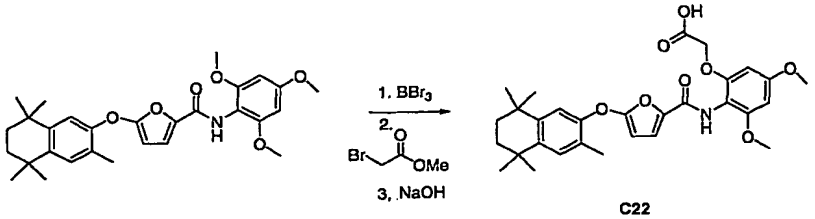
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (DMSO-d6): δ 1.24 (s, 6H), 1.70 (t, 2H, J = 5.76 Hz), 2.15 (s, 3H), 3.29 (t, 2H, J = 5.76 Hz), 3.83 (s, 9H), 5.15 (d, 1H, J = 3.59 Hz), 6.20 (s, 2H), 6.32 (s, 1H), 6.95 (s, 1H), 7.07 (d, 1H, J = 3.59 Hz), 7.18 (s, 1H), APCI-MS *m/z* 467 $(M+H)^+$.

Example C22: [3,5-dimethoxy-2-({5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]-2-furoyl}amino)phenoxy]acetic acid



C22

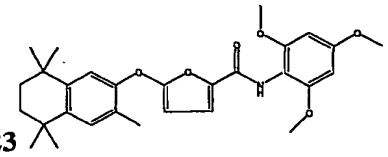
Compound C22 was synthesized in a manner analogous to that of C1, according to Scheme C, using similar starting compounds and reaction conditions. The particular procedure utilized is shown below:



C22

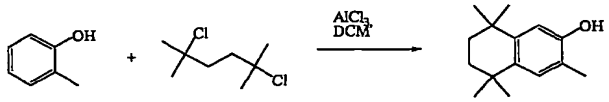
NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (CH3OD): δ 1.13(s, 6H), 1.19 (s, 6H), 1.59 (s, 4H), 2.13 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 4.57 (s, 2H), 5.21 (d, 1H, J = 3.78 Hz), 6.01 (d, 1H, J = 2.64 Hz), 6.12 (d, 1H, J = 2.64 Hz), 6.94 (s, 1H), 7.09 (d, 1H, J = 3.40 Hz), 7.15 (s, 1H), APCI-MS *m/z* 538 $(M+H)^+$.

Example C23: [(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-N(2,4,6-trimethoxyphenyl)-2-furamide



C23

Compound C23 was synthesized according to Scheme C. The requisite phenol was synthesized according the following method:



34 35 36

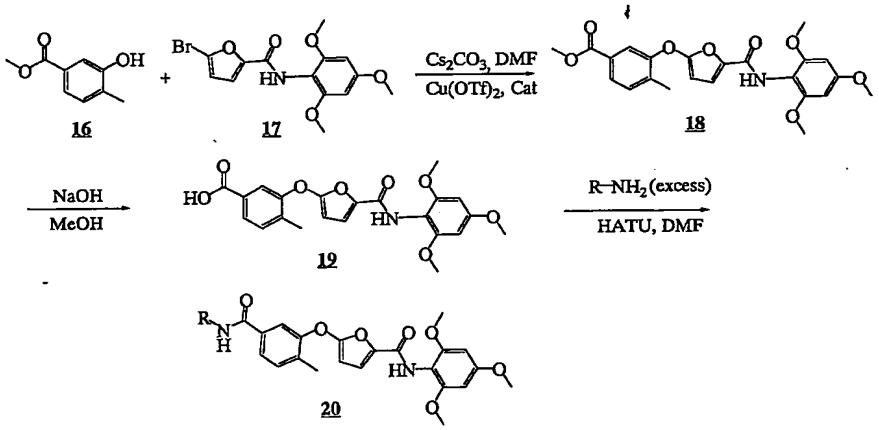
3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenol 36: A solution of *o*-cresol (17.3 g, 160 mmol), 2,5-dichloro-2,5-dimethylhexane (32.1 g, 175 mmol) in dichloromethane (80 mL) was stirred at 0°C under nitrogen as anhydrous $AlCl_3$ (2.34 g, 17.5 mmol) was added portionwise while keeping the temperature below 5°C. The suspension was allowed to warm to room temperature and further stirred for about 15 hours. The resulting white suspension was poured into ice water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The white solid thus obtained was recrystallized from toluene to give 28 g (80%) of the desired phenol. NMR data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 1.25 (s, 12H), 1.60 (s, 4H), 2.25 (s, 3H), 4.73 (s, 1H), 6.69 (s, 1H), 7.03 (s, 1H).

Compound C23: A suspension of phenol 36 (2.85 g, 13 mmol) and cesium carbonate (1.3 equiv., 4.24 g, 13 mmol) in anhydrous DMF (20 mL) was stirred at room temperature under nitrogen for 15 minutes before adding 5-Bromo-N-(2,4,6-trimethoxyphenyl)-2-furamide (3.57 g, 10 mmol) at once. The resulting suspension was stirred at 145 °C (bath temperature) for 18 hours. The progress of the reaction was monitored by TLC and FIMS. The suspension was quenched with cold water and

extracted several times with chloroform. The organic layer was washed with brine and water, dried (anhydrous sodium sulfate) and concentrated. The crude brown oil was further dried under high vacuum to remove last traces of solvents. The residue thus obtained was either recrystallized (Compound C23) from ether and dried overnight at 45 °C under vacuum to give title compound (60-65%) as a white solid which showed >95% purity by HPLC analysis. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.20 (s, 6H), 1.60 (s, 4H), 2.18 (s, 3H), 3.75 (s, 9H), 5.25 (d, 1H), 6.11 (s, 2H), 6.92 (s, 1H), 7.04 (d, 1H), 7.08 (s, 1H), 7.13 (br s, 1H), APCI-MS *m/z* 494.2 $(M+H)^+$.

The following compounds were prepared according to Scheme D set forth below:

Scheme D



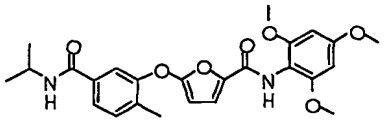
Condensation 18: A DMF solution (10 mL) containing 16 (0.365 g, 2.2 mmol), 17 (0.712 g, 2.0 mmol), cesium carbonate (0.716 g, 2.2 mmol), and copper triflate (0.036 g, 5 mol%), was heated at 100°C for 16 hours. DMF was then removed under reduced pressure. The crude was redissolved in ethylacetate and washed with 10%HCl, brine, dried (magnesium sulfate) and evaporated. The product 18 was purified by flash chromatography (1:1 EtOAc/Hexanes to EtOAc): 0.13 g.

Saponification 19: Compound 18 (0.126 g, .28 mmol) was saponified in methanolic NaOH. The reaction was monitored by TLC (1:1 EtOAc/Hexanes) and NaOH was added as needed. The reaction mixture was then concentrated. The crude was redissolved in water and extracted with diethyl ether. The aqueous layer was

acidified to pH 2-3 with concentrated HCl and extracted with methylene chloride. The methylene chloride extract was dried (magnesium sulfate) and evaporated to give the desired acid 19: 0.10 g.

HATU coupling 20: To a DMF solution (1 mL) containing 19 (0.056 g, .12 mmol) was added HATU (0.046 g, 0.121 mmol), and isopropylamine (9 molar excess). The reaction mixture was stirred at room temperature overnight. It was then diluted with ethyl acetate, washed with 10%HCl, saturated sodium bicarbonate, brine, dried (magnesium sulfate), and concentrated. The product 20 **(Compound D1)** was purified by prep TLC (5% MeOH in CH_2Cl_2): 0.019 g.

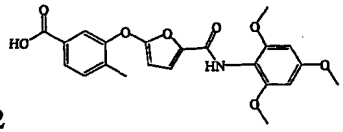
Example D1: 5-{5-[(isopropylamino)carbonyl]-2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



D1

Compound D1 was synthesized according to Scheme D above. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 6H), 2.36 (s, 3H), 3.85 (s, 9H), 4.25 (m, 1H), 5.44 (d, 1H), 5.91 (br d, 1H), 6.17 (s, 2H), 7.11 (d, 1H), 7.18 (s, 1H), 7.32 (d, 1H), 7.48 (d, 1H), 7.51 (s, 1H), MS (APCI $^+$): 469.1 $(M+H)^+$.

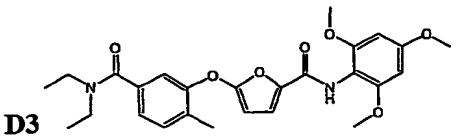
Example D2: 5-carboxy-(2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



D2

Compound D2 was synthesized in a manner analogous to that of D1, according to Scheme D. The yield of the purified product was 11%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (CDCl3): δ 2.39 (3H, s), 3.82 (9H, s), 5.48 (1H, d), 6.16 (2H, s), 7.14 (1H, d), 7.20 (1H, s), 7.35 (1H, d), 7.76 (1H, s), 7.85 (1H, d), FI-NCI m/z 426.1 (M-H).

Example D3: 5-{5-[(diethylamino)carbonyl]-2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide

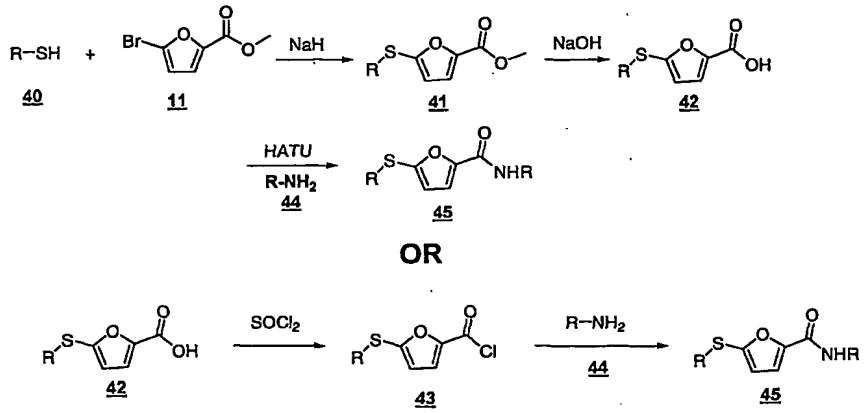


D3

Compound D3 was synthesized in a manner analogous to that of D1, according to Scheme D, with the exception that compound **18** was coupled with diethylamine to give Compound D3, 5-{5-[(diethylamino)carbonyl]-2-methylphenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (br, 6H), 2.38 (s, 3H), 3.28 (br, 2H), 3.50 (br, 2H), 3.82 (s, 9H), 5.51 (d, 1H), 6.18 (s, 2H), 7.05 (s, 1H), 7.15 (m, 3H), 7.28 (s, 1H), APCI-MS *m/z* 483.1 $(M+H)^+$.

Diarylthio ether analogs of the present invention, such as Compound F1, can be synthesized according to Scheme F shown and described below:

Scheme F



Methyl 5-thioaryl-2-furoate 41: A suspension of thiol **40** (1 mmol), NaH (60% dispersion in mineral oil, 1.1 mmol) in anhydrous N,N-dimethylacetamide (DMA, 3 mL/mmol) was heated under nitrogen at 60-70 °C with stirring for 30 minutes. A solution of methyl 5-bromo-2-furoate **11** (1 mmol) in anhydrous DMA (1 mL/mmol) was added dropwise to the hot solution. The temperature of the reaction mixture was gradually increased to 145°C. The reaction mixture was stirred at this temperature for an additional 15 hours. The solution was cooled and concentrated to about one quarter of its original volume *in vacuo* before adding to cold water (10 mL). The solution was extracted with ether (3 X 10 mL). The combined ether layer was washed with saturated $NaHCO_3$ (2 X 5 mL) and brine (2 X 5 mL), dried (Na_2SO_4) and

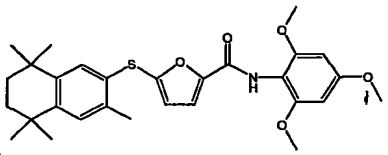
concentrated in vacuo to give pure methyl 5-thioaryl-2-furoate 41. Acidification of the aqueous layer resulted a mixture consisted of small amounts of 5-thioaryl-2-furoic acid and 5-bromo-2-furoic acid. Yield of 41: 40-75%.

Saponification 42: Compound 41 was saponified to the acid in ethanolic NaOH solution under similar reaction conditions as described above.

HATU coupling 45: The acid 42 was dissolved with DMF and coupled with the amine 44 under similar reaction conditions as described above to produce the Compound 45.

Acylhalide route 45: The acylhalide route via 43 can also be used to produce Compound 45.

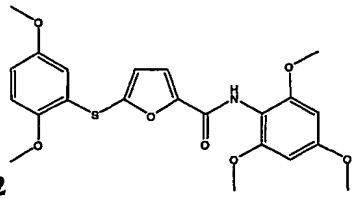
Example F1: 5-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)sulfanyl]-N-(2,4,6-trimethoxyphenyl)-2-furamide



F1

Compound F1 was synthesized according to Scheme F. The overall yield was 20%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 6H), 1.25 (s, 6H), 1.63 (s, 4H), 2.93 (s, 3H), 3.78 (s, 6H), 3.80 (s, 3H), 5.17 (br s, 2H, hydrated water), 6.14 (s, 2H), 6.58 (d, 1H), 7.12-7.13 (d, 2H), 7.24 (d, 1H), 7.46 (s, 1H), MS (APCI) m/z 510.1 $(M+H)^+$.

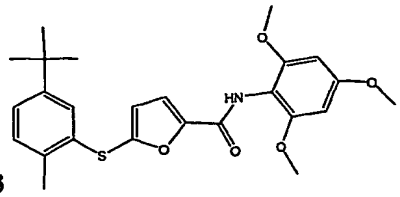
Example F2: 5-[(2,5-dimethoxyphenyl)sulfanyl]-N-(2,4,6-trimethoxyphenyl)-2-furamide



F2

Compound F2 was synthesized in a manner analogous to that of F1, according to Scheme F. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.82 (s, 6H), 3.83 (s, 3H), 3.89 (s, 3H), 6.18 (s, 2H), 6.54 (d, 1H), 6.75 (dd, 1H), 6.84 (d, 1H), 6.85 (d.1H), 7.28 (s, 1H), 7.49 (s, 1H), APCI-MS *m/z* 446.0 $(M+H)^+$. The overall yield was 45%.

Example F3: 5-{[5-(tert-butyl)-2-methylphenyl]sulfanyl}-N-(2,4,6-trimethoxyphenyl)-2-furamide

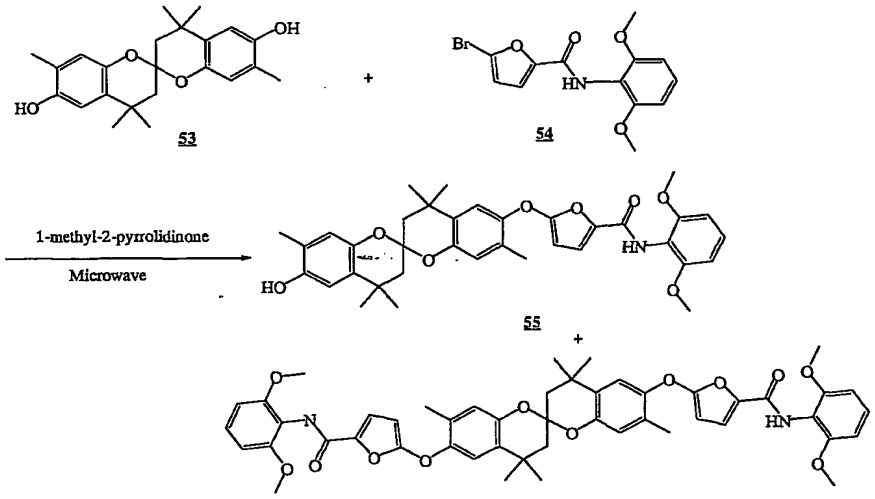


F3

Compound F3 was synthesized in a manner analogous to that of F1, according to Scheme F. The overall yield was 45%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 9H), 2.35 (s, 3H), 1.70 (s, 6H), 1.72 (s, 3H), 6.10 (s, 2H), 6.60 (d, 1H), 7.04 - 7.10 (m, 3H), 7.13 (d, 1H), 7.21 (s, 1H), APCI-MS *m/z* 456.1$(M+H)^+$.

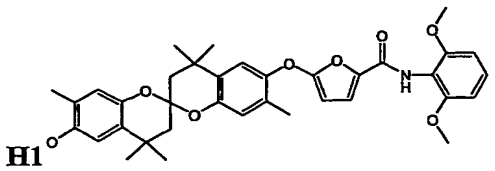
The following compounds were prepared according to Scheme H set forth below:

Scheme H



Synthesis of Compound 55: Phenol, bromide, and Cs2CO3 were semi-dissolved in minimum 1-methyl-2-pyrrolidinone. Mixture was placed in microwave for 2 minutes at 1100 W then allowed to cool for 1 minute before placing the mixture in microwave for an additional 2 minutes. Reaction was quenched with water/HCl and extracted with ethyl acetate.

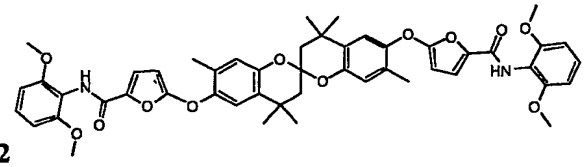
Example H1: N-(2,6-dimethoxyphenyl)-5-[(6'-hydroxy-4,4,4',4',7,7'-hexamethyl-2,2'-spirochromen-6-yl)oxy]-2-furamide



H1

Compound H1 was synthesized according to Scheme H. Purification was done by HPLC to give a 26% overall yield. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR, (MEOD): δ 1.30 (6H, s), 1.31 (6H, s), 1.56 (6H, s), 1.58 (6H, s), 1.92 - 1.98 (2H, dd, J = 4.35 Hz, 14.14 Hz), 2.03 (3H, s), 2.04 - 2.11 (2H, dd, J = 6.04 Hz, 14.14 Hz), 2.13 (3H, s), 3.82 (6H, s), 5.29 (1H, d, J = 3.77 Hz), 6.29 (1H, s), 6.52 (1H, s), 6.68 - 6.71 (2H, d, J = 8.69 Hz), 6.72 (1H, s), 7.13 (1H, s), 7.13 - 7.14 (1H, d, J = 2.61 Hz), 7.22-7.28 (1H, t, J = 8.50 Hz); m/z 614.

Example H2: 5-{[7-({5-[(2,6-dimethoxy anilino)carbonyl]-2-furyl}oxy)-4,4,4',4',7,7'-hexamethylbis-2,2'-spirochromen]oxy}-N-(2,6-dimethoxyphenyl)-2-furamide

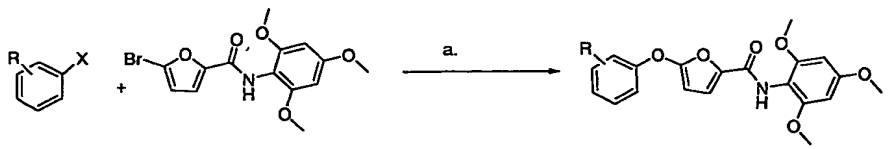


H2

Compound H2 was synthesized in a manner analogous to that of H1, according to Scheme H, using similar starting compounds and reaction conditions. The yield of the title product was 31%. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR, (MEOD): δ 1.34 (6H, s), 1.61 (6H, s), 1.99 - 2.04 (2H, d, J = 14.16 Hz), 2.14 (6H, s), 2.15 - 2.17 (2H, d, J = 14.16 Hz), 3.82 (12H, s), 5.31 (2H, d, J = 3.58 Hz), 6.55 (2H, s), 6.67-6.72 (4H, d, J = 8.49 Hz), 7.12-7.15 (2H, d, J = 3.58 Hz), 7.16 (2H, s), 7.22-7.28 (2H, t, J = 8.40 Hz); m/z 859.

The following compounds were synthesized via the phenol coupling procedure set forth below in Scheme I:

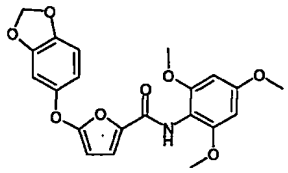
Scheme I



X is SH or OH
a. $CsCO_3$, DMF, microwave 220°C, 1minute; 180°C, 10minutes

To an empty glass tube (specifically manufactured for the Smith synthesizer), phenol (77.6 mgs, 0.421 mmol, 1.5 eq), 5-bromo-*N*-(2,4,6-trimethoxyphenyl)-2-furamide (100 mgs, 0.28 mmol, 1.0eq), and Cesium carbonate (183 mgs, 0.56 mmol, 2.0 eq) were suspended in 2.25 mL of anhydrous DMF. A Teflon coated stir bar was added. The tube was crimp-sealed and placed in the Smith Synthesizer microwave then heated for 1 minute at 220°C, and 10 minutes further at 180°C.

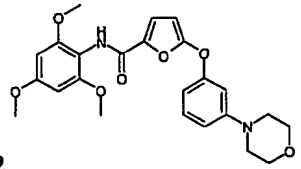
Example I1: 5-(1,3-benzodioxol-5-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I1

Compound I1 was synthesized by Scheme I. Product was purified by HPLC to yield compound in 10-50% yield. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 9H), 3.81 (s, 3H), 5.57 (d, 1H, J = 3.59 Hz), 5.99 (s, 2H), 6.26 (s, 2H), 6.67 (dd, 1H, J = 8.50, 2.27 Hz), 6.76 (dd, 1H, J = 2.27 Hz), 6.82 (d, 1H, J = 8.50 Hz), 7.13 (d, 1H, J = 2.64 Hz), Mass APCI 414.1.

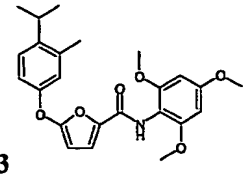
Example I2: 5-(3-morpholin-4-ylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I2

Compound I2 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.17 (t, 4H, J = 4.82 Hz), 3.79 (s, 9H), 3.81 (t, 4H), 5.66 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 6.63 (dd, 1H, J = 7.93, 1.89 Hz), 6.78 (t, 1H, J = 2.17 Hz), 6.84 (d, 1H, J = 7.93 Hz), 7.15 (d, 1H, J = 2.64 Hz), 7.27 (t, 1H, J = 8.22 Hz), Mass APCI 455.2.

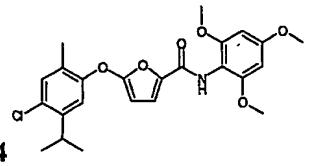
Example I3: 5-(4-isopropyl-3-methylphenoxy)-N-(2,4,6-trimethylphenyl)-2-furamide



I3

Compound I3 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.18 (m, 3H), 1.23 (s, 3H), 2.32 (s, 3H), 3.16 (t, 1H, J = 6.80 Hz), 3.79 (s, 6H), 3.81 (s, 3H), 5.59 (d, 1H, J = 3.40 Hz), 6.24 (s, 2H), 6.96 (m, 2H), 7.14 (s, 1H), 7.28 (d, 1H, J = 9.44 Hz), APCI 426.2.

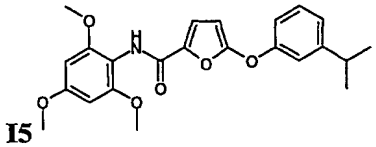
Example I4: 5-(4-chloro-5-isopropyl-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I4

Compound I4 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.20 (d, 6H, J = 6.99 Hz), 2.25 (s, 3H), 3.37 (m, 1H, J = 6.89 Hz), 3.78 (s, 6H), 3.83 (s, 3H), 5.46 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 7.06 (s, 1H), 7.15 (d, 1H, J = 2.83 Hz), 7.31 (s, 1H), Mass APCI 460.1.

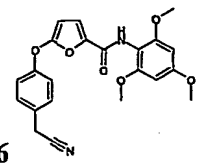
Example I5: 5-(3-isopropylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I5

Compound I5 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.23 (d, 6H, J = 6.99 Hz), 2.91 (q, 1H, J = 6.92 Hz), 3.77 (s, 6H), 3.80 (s, 3H), 5.64 (d, 1H, J = 3.59 Hz), 6.25 (s, 2H), 6.95 (d, 1H, J = 8.12 Hz), 7.04 (s, 1H), 7.10 (d, 1H, J = 7.74 Hz), 7.16 (s, 1H), 7.31 (t, 1H, J = 7.93 Hz), APCI mass 412.1.

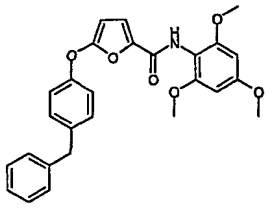
Example I6: 5-[4-(cyanomethyl)phenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I6

Compound I6 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.78 (s, 6H), 3.81 (s, 3H), 3.90 (s, 2H), 5.74 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 7.19 (t, 3H, J = 8.50 Hz), 7.42 (d, 2H, J = 8.69 Hz), APCI 409.1.

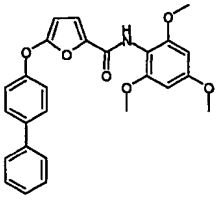
Example I7: 5-(4-benzylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I7

Compound I7 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.76 (s, 6H), 3.79 (s, 3H), 3.94 (s, 2H), 5.58 (d, 1H, J = 3.40 Hz), 6.24 (s, 2H), 7.14 (m, 10H), Mass APCI 460.1.

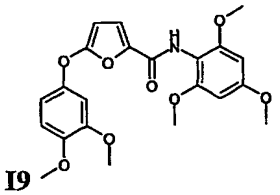
Example I8: 5-(1,1'-biphenyl-4-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I8

Compound I8 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (DMSO-d6): δ 3.71 (s, 6H), 3.78 (s, 3H), 5.94 (d, 1H, J = 3.59 Hz), 6.27 (s, 2H), 7.26 (d, 3H, J = 8.69 Hz), 7.36 (t, 1H, J = 7.27 Hz), 7.46 (dd, 2H, J = 7.74, 7.18 Hz), 7.65 (d, 2H, J = 7.37 Hz), 7.73 (d, 2H, J = 8.88 Hz), 8.97 (s, 1H), APCI mass 446.4.

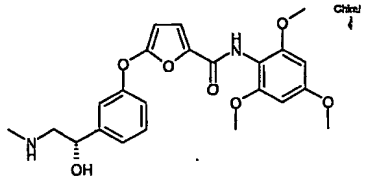
Example I9: 5-(3,4-dimethoxyphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I9

Compound I9 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 6H), 3.81 (s, 3H), 3.83 (s, 6H), 5.57 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 6.74 (dd, 1H, J = 8.69, 2.64 Hz), 6.87 (d, 1H, J = 2.64 Hz), 6.96 (d, 1H, J = 8.88 Hz), 7.14 (d, 1H, J = 2.64 Hz), APCI mass 430.2.

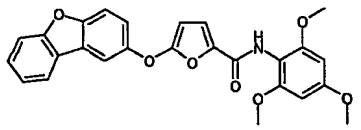
Example I10: 5-{3-[(1S)-1-hydroxy-2-(methylamino)ethyl]phenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



I10

Compound I10 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 2.73 (s, 3H), 3.11 (dt, 1H, J = 12.46, 9.82 Hz), 3.23 (m, 1H, J = 12.65, 9.25, 3.40, 3.40 Hz), 3.78 (s, 6H), 3.82 (s, 3H), 4.97 (dt, 1H, J = 9.63, 3.21 Hz), 5.76 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 7.17 (s, 2H), 7.29 (s, 2H), 7.45 (s, 1H), APCI mass 443.3.

Example I11: 5-(dibenzo[b,d]furan-2-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

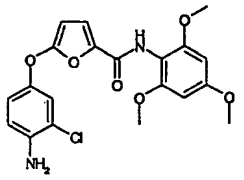


I11

Compound I11 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR

(CD_3OD): δ 3.76 (s, 6H), 3.78 (s, 3H), 5.62 (d, 1H, J = 3.40 Hz), 6.23 (s, 2H), 7.16 (d, 1H, J = 2.83 Hz), 7.30 (d, 1H, J = 5.29), 7.34 (d, 1H, J = 7.74 Hz), 7.48 (dd, 1H, J = 8.12, 7.18 Hz), 7.57 (dd, 2H, J = 8.50, 6.61 Hz), 7.83 (s, 1H), 7.97 (d, 1H, J = 7.74 Hz), Mass APCI 460.4.

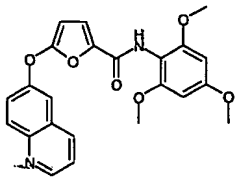
Example I12: 5-(4-amino-3-chlorophenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I12

Compound I12 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 6H), 3.81 (s, 3H), 5.52 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 6.89 (d, 1H, J = 8.88 Hz), 6.98 (d, 1H, J = 8.88 Hz), 7.13 (s, 1H), 7.15 (d, 1H, J = 2.64 Hz), Mass APCI 419.4.

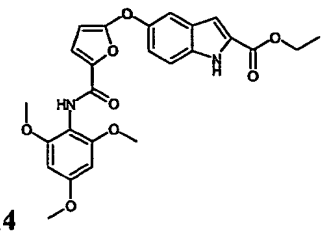
Example I13: 5-(quinolin-6-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I13

Compound I13 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.78 (s, 6H), 3.79 (s, 3H), 6.04 (d, 1H, J = 3.59 Hz), 6.24 (s, 2H), 7.28 (d, 1H, J = 3.02 Hz), 7.86 (m, 3H), 8.22 (d, 1H, J = 9.06 Hz), 8.81 (d, 1H, J = 8.31 Hz), 9.02 (d, 1H, J = 6.42 Hz), Mass APCI 422.1.

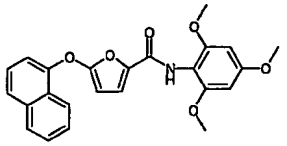
Example I14: Ethyl 7-[(5-{[(2,4,6-trimethoxyphenyl)amino]carbonyl}-2-furyl)oxy]-1H-indole-2-carboxylate



I14

Compound I14 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.40 (t, 3H, J = 7 Hz), 3.79 (s, 3H), 3.81 (s, 6H), 4.37 (q, 2H, J = 6.99 Hz), 5.49 (d, 1H, J = 3.4 Hz), 6.26 (s, 2H), 7.17 (m.3H), 7.48 (m, 2H), APCI mass 481.6.

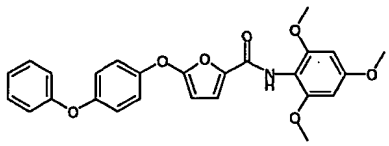
Example I15: 5-(1-Naphthyloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I15

Compound I15 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.80 (s, 6H), 3.81 (s, 3H), 5.66 (d, 1H, J = 3.59 Hz), 7.17 (d, 1H, J = 3.59 Hz), 7.23 (d, 1H, J = 7.74 Hz), 7.47 (t, 1H, J = 8.12 Hz), 7.57 (m, 2H), 7.75 (d, 1H, J = 8.12 Hz), 7.93 (m, 1H), 8.18 (m, 1H), APCI mass 421.0.

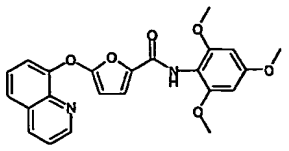
Example I16: 5-(4-phenoxyphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I16

Compound I16 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.78 (s, 6H), 3.81 (s, 3H), 5.65 (d, 1H, J = 3.59 Hz), 6.26 (s, 2H), 7.00 (m, 4), 7.10 (t, 1H, J = 7.37 Hz), 7.19 (m, 2H), 7.34 (dd, 2H, J = 8.50, 7.37 Hz), APCI mass 463.1.

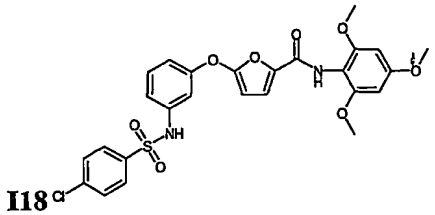
Example I17: 5-(quinolin-8-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I17

Compound I17 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 6H), 3.81 (s, 3H), 5.91 (d, 1H, J = 3.59 Hz), 6.25 (s, 2H), 7.23 (d, 1H, J = 3.02 Hz), 7.69 (d, 1H, J = 7.74 Hz), 7.78 (t, 1H, J = 8.03 Hz), 7.88 (t, 1H, J = 4.82 Hz), 7.99 (d, 1H, J = 8.31 Hz), 8.82 (d, 1H, J = 8.50 Hz), 9.04 (d, 1H, J = 4.72 Hz), APCI mass 421.8.

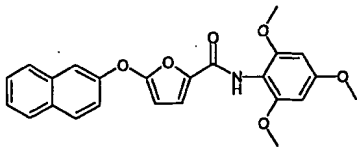
Example I18: 5-(3-{[(4-chlorophenyl)sulfonyl]amino}phenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I18

Compound I18 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 6H), 3.81 (s, 3H), 5.68 (d, 1H, J = 3.21 Hz), 6.26 (d, 1H, J = 3.21 Hz), 6.91 (m, 3H), 7.18 (d, 1H, J = 1.89 Hz), 7.26 (t, 1H, J = 8.40 Hz), 7.51 (d, 2H, J = 8.50 Hz), 7.74 (d, 2H, J = 8.31 Hz), APCI mass 559.5.

Example I19: 5-(2-naphthyloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

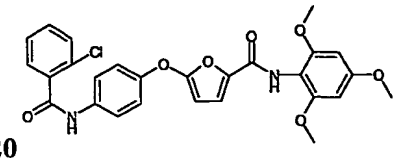


I19

Compound I19 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.78 (s, 3H), 3.83 (s, 6H), 5.77 (d, 1H, J = 3.59 Hz), 6.25 (s, 2H), 7.21 (s,

1H), 7.36 (dd, 1H, J = 9.06, 2.27 Hz), 7.48 (m, 2H), 7.58 (s, 1H), 7.83 (d, 1H, J = 7.74 Hz), 7.88 (d, 1H, J = 7.74 Hz), 7.95 (d, 1H, J = 8.88 Hz), APCI mass 420.9.

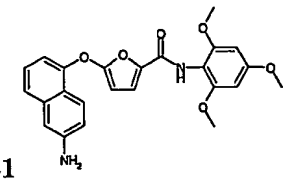
Example I20: 5-{4-[(2-chlorobenzoyl)amino]phenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



I20

Compound I20 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (DMSO-d6): δ 3.71 (s, 6H), 3.78 (s, 3H), 5.79 (d, 1H, J = 3.40 Hz), 6.27 (s, 2H), 7.23 (m, 3H), 7.52 (m, 3H), 7.78 (m, 2H), 8.93 (s, 1H), 10.59 (s, 1H), APCI mass 523.6.

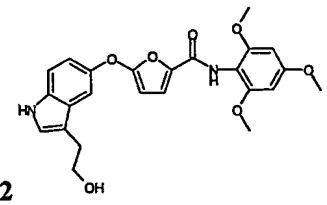
Example I21: 5-{(6-amino-1-naphthyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I21

Compound I21 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 4.52 (s, 6H), 4.59 (s, 3H), 6.61 (d, 1H, J = 3.40 Hz), 7.08 (s, 2H), 7.67 (d, 1H, J = 7.55 Hz), 7.85 (s, 1H), 7.91 (dd, 1H, J = 9.07, 2.27 Hz), 8.04 (s, 1H), 8.12 (t, 1H, J = 7.93 Hz), 8.27 (d, 1H, J = 8.31 Hz), 8.72 (d, 1H, J = 9.07 Hz), 9.77 (s, 1H), APCI mass 435.1.

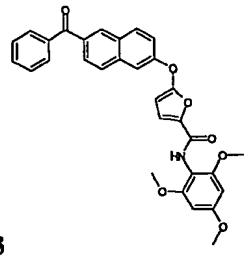
Example I22: 5-{[3-(2-hydroxyethyl)-1H-indol-7-yl]oxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide



I22

Compound I22 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (DMSO-d6): δ 2.80 (d, 2H, J = 6.99 Hz), 3.61 (t, 2H, J = 7.18 Hz), 3.72 (s, 6H), 3.79 (s, 3H), 5.53 (d, 1H, J = 3.59 Hz), 6.27 (s, 2H), 6.96 (d, 1H, J = 8.69 Hz), 7.16 (s, 1H), 7.23 (s, 1H), 7.35 (s, 1H), 7.37 (d, 1H, J = 9.06 Hz), 8.87 (s, 1H), 10.94 (s, 1H), APCI mass 453.1.

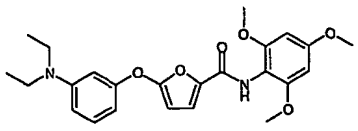
Example I23: 5-[(6-benzoyl-1-naphthyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I23

Compound I23 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (dmso-d6): δ 3.71 (s, 6H), 3.79 (s, 3H), 6.07 (d, 1H, J = 3.40 Hz), 6.27 (s, 1H), 7.52 (d, 1H, J = 9.07 Hz), 7.59 (dd, 2H, J = 7.55, 7.18 Hz), 7.70 (dd, 1H, J = 7.55, 7.18 Hz), 7.76 (m, 1H), 7.81 (d, 2H, J = 7.18 Hz), 7.89 (d, 1H, J = 8.31 Hz), 8.10 (d, 1H, J = 8.69 Hz), 8.24 (d, 1H, J = 9.07 Hz), 8.36 (s, 1H), 9.01 (s, 1H), APCI mass 524.2.

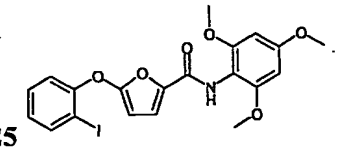
Example I24: 5-[3-(diethylamino)phenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I24

Compound I24 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.15 (t, 6H, J = 7.18 Hz), 3.50 (t, 4H, J = 7.18 Hz), 3.78 (s, 6H), 3.82 (s, 3H), 5.77 (d, 1H, J = 3.02 Hz), 6.26 (s, 2H), 6.84 (s, 3H), 7.19 (s, 1H), 7.38(t, 1H, J = 8.31 Hz), APCI mass 441.1.

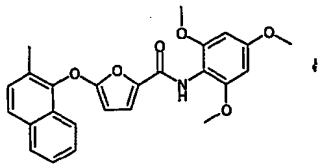
Example I25: 5-(2-iodophenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I25

Compound I25 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 3.79 (s, 6H), 3.82 (s, 3H), 5.57 (d, 1H, J = 3.40 Hz), 6.26 (s, 2H), 7.02 (t, 1H, J = 7.55 Hz), 7.16 (s, 1H), 7.20 (d, 1H, J = 8.69 Hz), 7.43 (dd, 1H, J = 6.80, 1.51 Hz), 7.91 (dd, 1H, J = 7.93, 1.51 Hz), APCI mass 496.1.

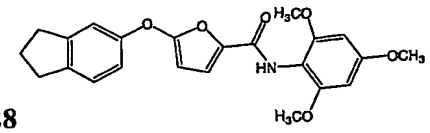
Example I26: 5-[(2-methyl-1-naphthyl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I26

Compound I26 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (dmso-d6): δ 2.38 (s, 3H), 3.70 (s, 6H), 3.81 (s, 3H), 5.06 (d, 1H, J = 3.40 Hz), 6.28 (s, 2H), 7.10 (s, 1H), 7.54 (m, 3H), 7.87 (d, 2H, J = 8.31 Hz), 7.99 (d, 1H, J = 8.31 Hz), 8.91 (s, 1H), APCI mass 434.1.

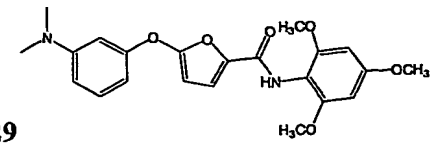
Example I28: 5-(2,3-dihydro-1H-inden-5-yloxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I28

Compound I28 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 2.10 (m, 2H, J = 7.37, 7.55, 7.37, 7.37 Hz), 2.89 (q, 4H, J = 7.49 Hz), 3.78 (s, 6H), 3.82 (s, 3H), 5.56 (d, 1H, J = 3.40 Hz), 6.26 (s, 2H), 6.92 (d, 1H, J = 8.12 Hz), 7.02 (s, 1H), 7.13 (s, 1H), 7.22 (d, 1H, J = 8.12 Hz), APCI mass 410.1.

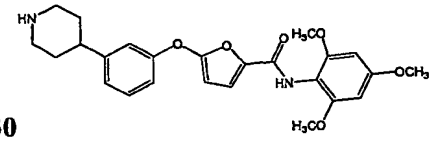
Example I29: 5-[3-(dimethylamino)phenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I29

Compound I29 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 2.99 (s, 6H), 3.77 (s, 6H), 3.82 (s, 3H), 5.69 (d, 1H, J = 3.59 Hz), 6.26 (s, 1H), 6.60 (d, 1H, J = 8.12 Hz), 6.69 (s, 1H), 6.76 (d, 1H, J = 8.31 Hz), 7.16 (d, 1H, J = 2.83 Hz), 7.28 (t, 1H, J = 8.22 Hz), APCI mass 413.1.

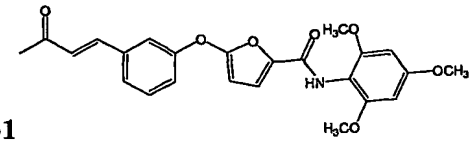
Example I30: 5-(3-piperidin-4-ylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



I30

Compound I30 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 1.87 (t, 2H, J = 12.84 Hz), 2.09 (d, 2H, J = 13.98 Hz), 2.95 (m, 1H, J = 12.09, 11.33, 3.78, 3.40 Hz), 3.12 (dd, 2H, J = 12.84, 12.09 Hz), 3.49 (d, 2H, J = 10.95 Hz), 3.77 (s, 6H) 3.82 (s, 3H), 5.70 (d, 1H, J = 3.02 Hz), 6.25 (s, 2H), 7.12 (M, 3H), 7.39 (M, 1H), APCI mass 453.2.

Example I31: 5-{4-[(1E)-3-oxobut-1-enyl]phenoxy}-N-(2,4,6-trimethoxyphenyl)-2-furamide

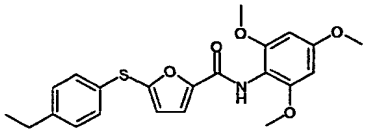


I31

Compound I31 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR (CD_3OD): δ 2.37 (s, 3H), 3.77 (s, 6H), 3.83 (s, 3H), 5.85 (d, 1H, J = 3.40 Hz), 6.27 (s,

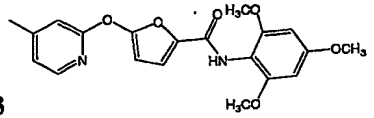
2H), 6.76 (d, 1H, J = 16.24 Hz), 7.13 (bs, 1H), 7.21 (d, 2H, J = 6.23 Hz), 7.62 (d, 1H, J = 16.24 Hz), 7.74 (s, 2H), APCI mass 438.1.

Exmple I32: 5-(4-Ethyl-phenylsulfanyl)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



I32

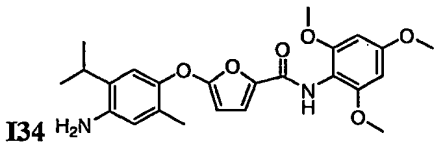
Example I33: 5-[(4-methylpyridin-2-yl)oxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I33

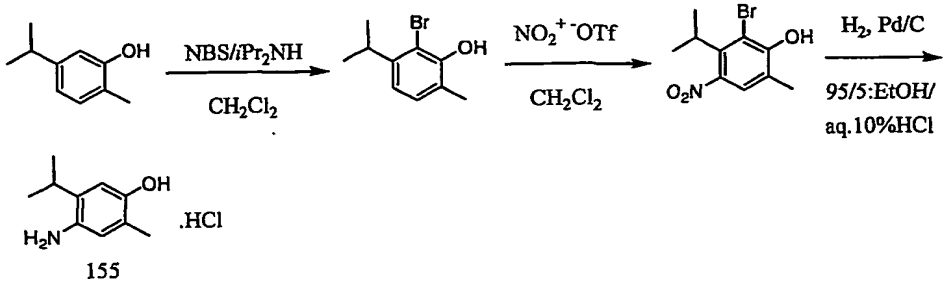
Compound I33 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}HNMR ($CDCl_3$): δ 2.27 (s, 3H), 3.77 (s, 6H), 3.84 (s, 3H), 6.27 (s, 2H), 6.38 (d, 1H, J = 7.18 Hz), 6.46 (s, 1H), 6.92 (s, 1H), 7.29 (s, 1H), 8.02 (d, 1H, J = 6.80 Hz), APCI mass 385.1.

Example I34: 5-(4-amino-5-isopropyl-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



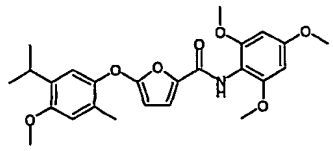
I34

Compound I34 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d), 2.17 (3H, s), 2.86 (1H, hep), 3.60 (2H, br s), 3.82 (9H, s), 5.15 (1H, d), 6.18 (2H, s), 6.54 (1H, s), 6.90 (1H, s), 7.07 (1H, d), 7.18 (1H, s), FI-PCI m/z 441.2 $(M+H)^+$.



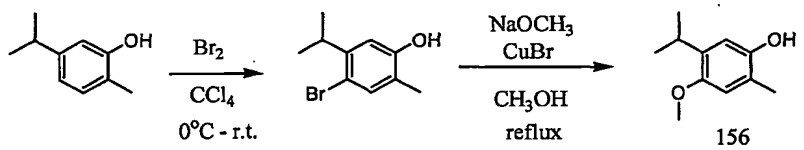
155

Example I35: 5-(5-isopropyl-4-methoxy-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



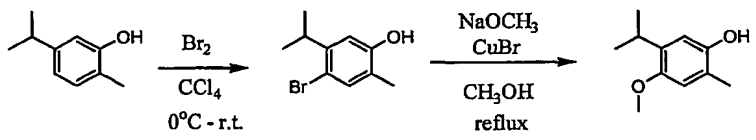
I35

Compound I35 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions.



156

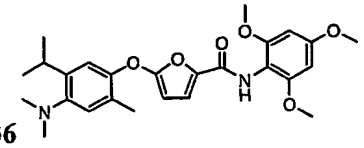
I35



To a carbon tetrachloride solution (25 mL) containing 5-isopropyl-2-methylphenol (1.5 g, 10 mmol) was added bromine (.550 mL, 10 mmol) dropwise at 0°C. The mixture was allowed to warm to r.t. and was stirred overnight. It was diluted with dichloromethane, washed with aq. Sodium bicarbonate, brine, dried (magnesium sulfate) and evaporated to a liquid: 2.41 g (94%). ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, d), 2.18 (3H, s), 3.22 (1H, hep), 4.66 (1H, s), 6.69 (1H, s), 7.25 (1H, s). To a RB flask was charged with 4-bromo-5-isopropyl-2-methylphenol (1.82 g, 8 mmol), ethylacetate (.7 mL), cuprous bromide (.23 g, 1.6 mmol), and 25 wt% (~5M) sodium methoxide in methanol (16 mL). The mixture was heated gradually in an oil bath to reflux (oil bath temperature 90-95oC) under argon atmosphere for 16 h. After cooling to r.t., the

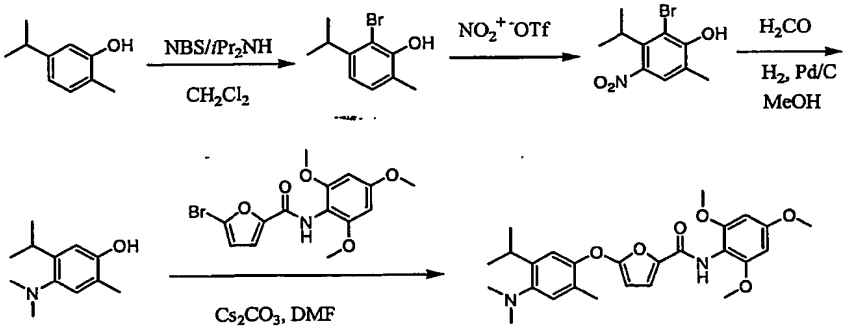
reaction mixture was acidified with conc. HCl to pH 2. The acidified mixture was concentrated on a rotovap. The aqueous solution was extracted with diethyl ether 3 times. The combined ether extracts were washed with brine, dried over magnesium sulfate, and evaporated to an orange-colored liquid. The desired product was purified by flash chromatography (eluting solvents: hexanes to 10% ethylacetate in hexanes): 1.05 g (73%). ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, d), 2.42 (3H, s), 3.42 (1H, hep), 3.95 (3H, s), 4.80 (1H, s), 6.83 (1H, s), 6.84 (1H, s). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.16 (6H, d), 2.25 (3H, s), 3.52 (1H, hep), 3.82 (12H, s), 5.21 (1H, d), 6.18 (2H, s), 6.71 (1H, s), 7.0 (1H, s), 7.12 (1H, d), 7.19 (1H, s), FI-PCI m/z 456.2 $(M+H)^+$.

Example I36: 5-[4-(dimethylamino)-5-isopropyl-2-methylphenoxy]-N-(2,4,6-trimethoxyphenyl)-2-furamide



I36

Compound I36 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. The specific method utilized for the synthesis of I36 is depicted as follows:



Bromination: A solution of 5-isopropyl-2-methylphenol (3.0 g, 20 mmol) in methylene chloride (5 mL) was mixed with diisopropylamine (.280 mL, 2 mmol) in a 500 mL RB flask. To this mixture was added dropwise a solution of N-bromosuccinimide (3.56 g, 20 mmol) in methylene chloride (120 mL). The reaction mixture was stirred at room temperature overnight. It was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate and the solvent was then evaporated to give the product 6-bromo-5-isopropyl-2-methylphenol: liquid, 4.22 g

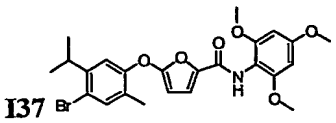
(92.6%). NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d), 2.26 (3H, s), 3.27 (1H, hep), 5.73 (1H, s), 6.75 (1H, d), 7.02 (1H, d).

Nitration: Into a RB flask containing a stirred suspension of tetramethylammonium nitrate (96%, Aldrich) (1.288 g, 9.07 mmol) in anhydrous methylene chloride (25 mL) was added trifluoromethane sulfonic anhydride (1.58 mL/2.65 g, 9.31 mmol) dropwise at room temperature, under argon. The suspension was stirred at room temperature for 1.5 hours. The flask was then placed in a dry ice/acetone cold bath. A methylene chloride solution (10 mL) of 6-bromo-5-isopropyl-2-methylphenol (1.96 g, 8.63 mmol) was added via a syringe. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. It was diluted with methylene chloride, washed with water until neutral pH was reached, followed by brine, dried (magnesium sulfate) and evaporated. The product 6-bromo-4-nitro-5-isopropyl-2-methylphenol was purified by flash chromatography on silica gel (eluting solvent: 1 ethyl acetate/5 hexanes): 0.60 g, (25.4%). NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.40 (6H, d), 2.30 (3H, s), 3.50 (1H, hep), 6.21 (1H, s), 7.36 (1H, s).

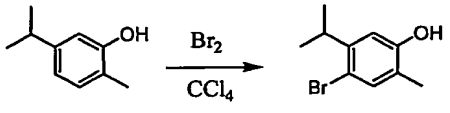
Hydrogenation: A mixture of 6-bromo-4-nitro-5-isopropyl-2-methylphenol (0.60 g, 2.19 mmol), formaldeyde solution (40% aqueous solution, 700 mL, 8.80 mmol), 10% palladium on carbon (0.2 g), in methanol (20 mL) was hydrogenated in a Parr apparatus at 45 psi for 16 hours. The mixture was then filtered through a pad of Celite. The filtrate was concentrated on a rotovap to give the product 4-N,N-dimethylamino-5-isopropyl-2methylphenol. HBr as a dark solid residue: 0.522 g (87%). NMR and mass spectrometry data consistent with the desired title product is as follows: ^{1}H NMR ($CDCl_3$): δ 1.28 (6H, d), 2.25 (3H, s), 3.22 (6H, s), 3.80 (1H, hep), 5.85 (1H, br s), 6.92 (1H, s), 7.18 (1H, s).

Phenol coupling: The microwave protocol of Scheme I was followed. Condition: DMF, 200°C, 2x10 minutes. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$): δ 1.16 (6H, d), 2.25 (3H, s), 2.66 (6H, s), 3.52 (1H, hep), 3.82 (9H, s), 5.30 (1H, d), 6.18 (2H, s), 6.96 (2H, s), 7.12 (1H, d), 7.21 (1H, s), FI-PCI m/z 469.2 $(M+H)^+$.

Example I37: 5-(4-bromo-5-isopropyl-2-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide

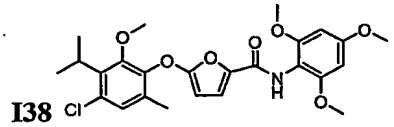


Compound I37 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions.

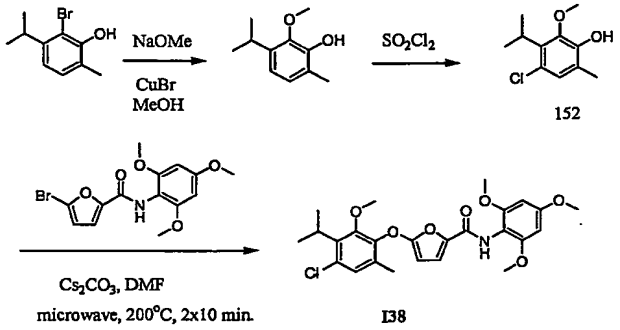


To a carbon tetrachloride solution (25 mL) containing 5-isopropyl-2-methylphenol (1.5 g, 10 mmol) was added bromine (.550 mL, 10 mmol) dropwise at 0°C. The mixture was allowed to warm to r.t. and was stirred overnight. It was diluted with dichloromethane, washed with aq. Sodium bicarbonate, brine, dried (magnesium sulfate) and evaporated to a liquid: 2.41 g (94%). ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, d), 2.18 (3H, s), 3.22 (1H, hep), 4.66 (1H, s), 6.69 (1H, s), 7.25 (1H, s). NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (DMSO-d_6): δ 1.09 (6H, d), 2.15 (3H, s), 3.13 (1H, hep), 3.65 (6H, s), 3.7 (3H, s), 5.54 (1H, d), 6.20 (2H, s), 7.07 (1H, s), 7.12 (1H, br d), 7.53 (1H, s), 8.85 (1H, br s). FI-PCI m/z 504.1, 506.0 $(M+H)^+$.

Example I38: 5-(4-chloro-3-isopropyl-2-methoxy-6-methylphenoxy)-N-(2,4,6-trimethoxyphenyl)-2-furamide



Compound I38 was made in a manner analogous to I1, according to Scheme I, using similar starting compounds and reaction conditions. The specific method utilized for the synthesis of I38 is depicted as follows:

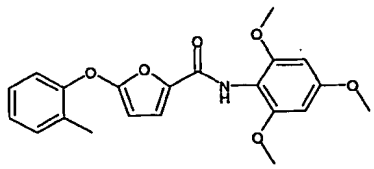


Displacement of bromine by methoxide: A mixture consisting of 6-bromo-5-isopropyl-2-methylphenol (2.28 g, 10 mmol), ethyl acetate (0.8 mL), cuprous bromide (0.286 g, 2 mmol), and a 25wt% solution of sodium methoxide (20 mL) was heated at reflux (oil bath 90 – 95°C) under argon for 16 hours. The reaction mixture was cooled to room temperature, and was acidified with concentrated HCl to pH 2-3. The mixture was then diluted with methanol and filtered through Celite. The filtrate was concentrated. The concentrate was redissolved in diethyl ether, washed with aqueous 10% HCl, brine, dried (magnesium sulfate), and evaporated to a solid residue 6-methoxy-5-isopropyl-2-methylphenol: 1.5 g (83%). NMR data consistent with the desired title product is as follows: ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d), 2.22 (3H, s), 3.23 (1H, hep), 3.78 (3H, s), 5.64 (1H, s), 6.68 (1H, d), 6.85 (1H, d).

Chlorination: Sulfuryl chloride (.442 mL, 5.5 mmol) was added to a chloroform solution (25 mL) of 6-methoxy-5-isopropyl-2-methylphenol (1.05 g, 5 mmol). The reaction mixture was heated at 60°C for 2 hours, then was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate and evaporated to an oil (1.33 g). The product 6-methoxy-4-chloro-5-isopropyl-2-methylphenol was purified by flash chromatography on silica gel: 1.03 g (96%). NMR data consistent with the title product were as follows: ^{1}H NMR ($CDCl_3$) □ 1.41 (6H, d), 2.19 (3H, s), 3.51 (1H, hep), 3.76 (3H, s), 5.53 (1H, s), 6.88 (1H, s).

Phenol coupling: The microwave protocol of Scheme I was followed. Condition: DMF, 200°C, 2x10 minutes. NMR and mass spectrometry data consistent with the title product were as follows: ^{1}H NMR (MeOD-d_4): δ 1.35 (6H, d), 2.21 (3H, s), 3.61 (1H, hep), 3.80 (6H, s), 3.81 (3H, s), 3.85 (3H, s), 5.16 (1H, d), 6.26 (2H, s), 7.10 (2H, s), FI-PCI m/z 490.1, 492.1 $(M+H)^+$.

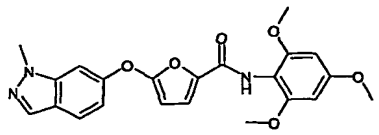
Example I39: 5-o-Tolyloxy-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



I39

Compound I39 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

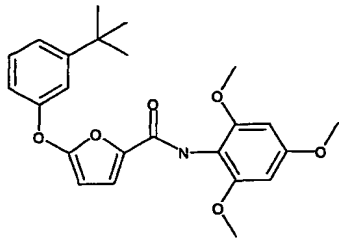
Example I40: 5-(1-Methyl-1H-indazol-6-yloxy)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



I40

Compound I40 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

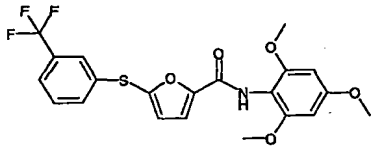
Example I41: 5-(3-tert-Butyl-phenoxy)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



I41

Compound I41 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

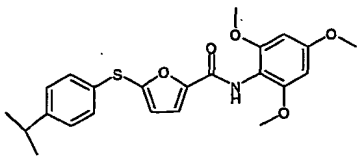
Example I42: 5-(3-Trifluoromethyl-phenylsulfanyl)-furan-2-carboxylic acid (2,4,6 trimethoxy-phenyl) -amide



I42

Compound I42 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

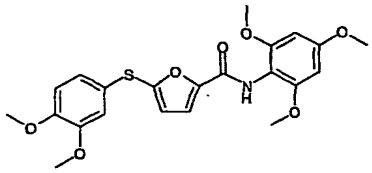
Example I43: 5-(4-Isopropyl-phenylsulfanyl)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide



I43

Compound I43 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

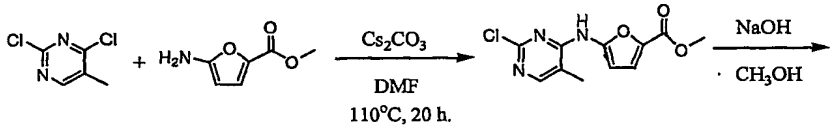
Example I44: 5-(3,4-Dimethoxy-phenylsulfanyl)-furan-2-carboxylic acid (2,4,6-trimethoxy-phenyl)-amide

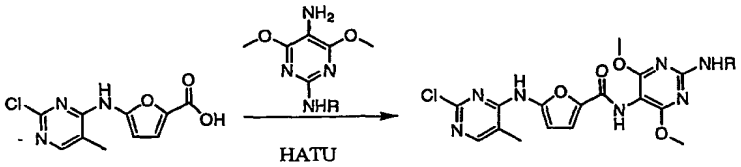


I44

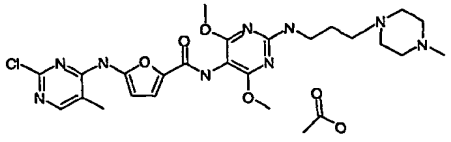
Compound I44 was synthesized in a manner analogous to compound I1, according to scheme I, using similar starting materials and reaction conditions.

Scheme J





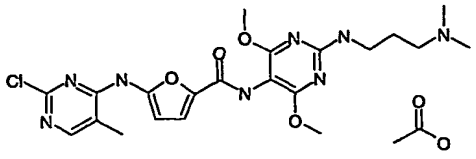
Example J1: 5-[(2-chloro-5-methylpyrimidin-4-yl)amino]-N-(4,6-dimethoxy-2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)-2-furamide acetate



J1

Compound JI was synthesized according to scheme J, using similar starting materials and reaction conditions.

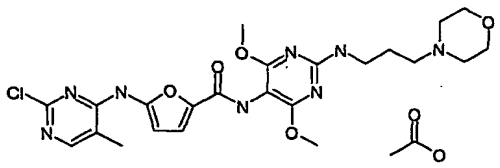
Exmaple J2: 5-[(2-chloro-5-methylpyrimidin-4-yl)amino]-N-(2-{[3-(dimethylamino)propyl]amino}-4,6-dimethoxypyrimidin-5-yl)-2-furamide acetate



J2

Compound J2 was synthesized according to scheme J, using similar starting materials and reaction conditions.

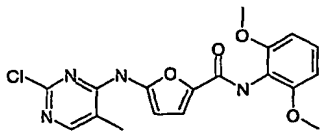
Example J3: 5-[(2-chloro-5-methylpyrimidin-4-yl)amino]-N-{4,6-dimethoxy-2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}-2-furamide acetate



J3

Compound J3was synthesized according to scheme J, using similar starting materials and reaction conditions.

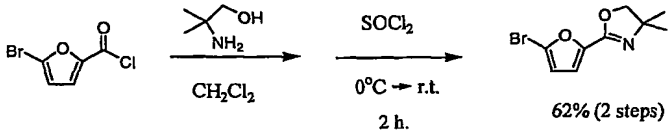
Exmaple J4: 5-[(2-chloro-5-methylpyrimidin-4-yl)amino]-N-(2,6-dimethoxyphenyl)-2-furamide

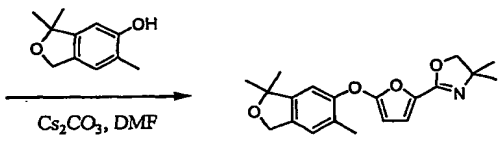


J4

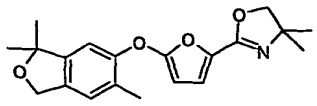
Compound J4 was synthesized according to scheme J, using similar starting materials and reaction conditions.

Scheme K





Example K1: 4,4-Dimethyl-2-[5-(3,3,6-trimethyl-1,3-dihydro-isobenzofuran-5-yloxy)-furan-2-yl]-4,5-dihydro-oxazole



K1

Compound K1 was synthesized according to scheme K.

Biological Testing And Enzyme Assays

In Vitro Assays:

Assessment of GnRH Receptor Activation Using Microphysiometry

By performing exemplary assays described below, the functionality of the compounds of the invention as GnRH antagonists may be confirmed.

Materials and Methods.

GnRH, Ac-D-2-Nal-p-chloro-D-Phe-β-(3-pyridyl)-D-Ala-Ser-Lys(nicotinoyl)-D-Lys(nicotinoyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH_2 (antide), the superagonist peptide [D-Ala^6, des-Gly^{10}]proethylamide^9-LHRH (GnRH-A), and TRH may be purchased from Bachem (Torrance, CA). Cell Culture media and forskolin may be purchased from Sigma (St. Louis, MO). Fetal bovine serum (FBS) and penicillin/streptomycin are available from Omega Scientific, Inc. (Tarzana, CA). G418 may be obtained from Gemini (Calabasas, CA). Staurosporine, Rp-adenosine 3',5'-cyclic monophosphothioate triethylamine (Rp-cAMPS), PMA, and 5-(N-methyl-N-isobutyl)-amiloride (MIA) are available from RBI (Natick, MA). 2-[1-(3-Dimethylaminopropyl)indol-3-yl]-3-(indol-3-yl)maleimide (GF 109203X) may be purchased from Tocris (Ballwin, MO).

Cell Culture. GGH_3 cells (Dr. William Chin, Harvard Medical School, Boston, MA) are grown in low glucose Dulbecco's modified Eagle's medium (DMEM) containing 100U/mL penicillin/streptomycin, 0.6 g/L G418 and 10% heat-inactivated FBS.

Total Inositol Phosphates Measurement.

The activity of various GnRH peptide agonists is initially assessed utilizing an assay that measures accumulation of total inositol phosphates. Approximately 200,000 GGH_3 cells/well are plated onto 24-well tissue culture plates using DMEM media. The following day, cells are loaded with [^{3}H]myoinositol (0.5 Ci/ml) for 16-18

hours in inositol-free medium. The medium is aspirated and the cells rinsed with serum-free DMEM. Cells are stimulated with GnRH (0.1 nM—1 μM) or the superagonist, GnRH-A (0.01 nM–100 nM) dissolved in DMEM media in a total volume of 1 mL containing 10 mM LiCl at 37°C for 45 minutes. The media is replaced with 1 mL ice-cold 10 mM formic acid, which stops the reaction and also serves to extract cellular lipids. Inositol phosphates are separated by ion-exchange chromatography on Dowex columns, which are washed with 2.5 mL of 10 mM myoinositol and 10 mM formic acid. The columns are then washed with 5 mL of 60 mM sodium formate and 5 mM borax, and total inositol phosphates are eluted with 5 mL 1M ammonium formate, 0.1 M formic acid. The column eluates are added to liquid scintillation vials containing 15 ml of scintillation cocktail and are counted by liquid scintillation counting.

Preparation of ^{125}I-GnRH-A radioligand.

The radioiodinated agonist analog of GnRH, ^{125}I-GnRH-A, is used as the radioligand. One μg of GnRH-A diluted in 0.1M acetic acid is added to an Iodogen®-coated borosilicate glass tube (Pierce) containing 35 μl of 0.05 M phospate buffer (pH 7.4-7.6) and 1 mCi of Na[^{125}I]. The reaction mixture is vortexed and incubated for 1 min at room temperature. 2 ml of 0.5 M acetic acid is added to the reaction tube and the mixture is added to a C18 Sep-Pak cartridge. The cartridge is washed with subsequent washes of 5 ml H_2O and 5 ml 0.5M acetic acid and then eluted with 5 x 1 ml of 60% CH_3CN/40% 0.5M acetic acid. The eluate is diluted with 3x volume of HPLC buffer A (0.1% TFA in H_2O) and loaded onto a C18 column. The iodinated product is eluted over 20-25 min with a gradient of 25-100% CH_3CN containing 0.1%TFA. The radioactive fractions (750 μl/fraction) are collected into clean polypropylene tubes containing 100 μl of 10% BSA. Fractions are assessed for biological activity by radioligand binding.

Competition Radioligand Binding.

Approximately two million GGH_3 cells/tube are utilized for radioligand binding. ^{125}I-GnRH-A (approximately 0.1-0.3 nM) is incubated with cells in the presence or absence of competing agents in a final volume of 300 μl binding assay buffer [50 mM HEPES (pH 7.4), 1 mM EDTA, 2.5 mM $MgCl_2$, and 0.1% BSA] to test the ability of compounds to displace agonist binding. Reactions are performed on ice for 2 hr and stopped by the addition of 2 ml of ice-cold PBS wash buffer (50 mM

$NaPO_4$, 0.9% NaCl, 2 mM $MgCl_2$, and 0.02% NaN_3, pH 7.4) and rapid filtration onto GF/C filters presoaked with 0.05% polyethylenimine utilizing a Brandel cell harvester. Filters are counted on a gamma counter.

Microphysiometry.

The Cytosensor® Microphysiometer (Molecular Devices, Sunnyvale, CA) is a real-time, noninvasive, nonradioactive semiconductor-based system for monitoring the cellular responses to various stimuli. It is based on a pH-sensitive silicon sensor, the light-addressable potentiometric sensor which forms part of a microvolume flow chamber in which cultured cells are immobilized (14, 15, 17). GGH_3 cells are seeded in low-buffered minimal essential media (MEM, Sigma) containing 25 mM NaCl and 0.1% BSA at a density of 500,000 cells/capsule onto the polycarbonate membrane (3 μm porosity) of cell capsule cups (Molecular Devices, Sunnyvale, CA). Capsule cups are transferred to sensor chambers where cells are held in close apposition to a silicon sensor within a sensor chamber, which measures small changes in pH in the microvolume of the sensor chamber. Low-buffered medium is pumped continuously across the cells at a rate of approximately 100 μl/min from one of two fluid reservoirs. A selection valve determines which reservoir from which fluid is perfused onto the cells.

The Cytosensor®Microphysiometer generates a voltage signal, which is a linear function of pH, every second. In order to measure acidification rates, flow to the sensor chamber containing the cells is periodically interrupted, allowing excreted acidic metabolites to build up in the extracellular fluid of the cells. Cells are maintained at 37 °C on a two-minute flow cycle with cells being perfused with media for 80 seconds followed by 40 seconds in which the flow of media is stopped. During this 40-second interval, acidification rates are measured for a 30 sec interval. In this fashion, a single acidification rate is calculated every two min. The Cytosensor® Microphysiometer device contains eight such sensor units, allowing for eight simultaneous experiments to be performed. Each unit is individually programmed utilizing a computer linked to the system.

GGH_3 cells are initially equilibrated in the low-buffered MEM media for a period of 30-60 min in which basal acidification rates (measured as μV/sec), in the absence of any stimuli, are monitored. When the basal rate of acidification changes by less than ten percent over a period of twenty minutes, experiments are initiated.

Time course experiments are performed to determine the optimal time for agonist exposure prior to acidification rate measurement and the duration of exposure needed to obtain peak acidification responses to various agonists. From these time course experiments, it has been determined that cells should be exposed to GnRH peptide agonists at least one minute prior to collection of acidification rate data. Peak acidification rates usually occur in the first two-min exposure cycle. When the effects of various inhibitors are measured, cells are pretreated for 20 min with test compound diluted in low-buffered MEM containing 1% DMSO final concentration prior to exposure of the cells for 4 min to a solution containing GnRH or PMA at appropriate concentration in the presence of inhibitor.

Cyclic AMP Measurement.

The ability of various compounds to increase basal cAMP formation in GGH_3 cells is assessed utilizing 96-well adenylyl cyclase flashplates purchased from New England Nuclear (NEN, Boston, MA). Cells (approximately 50,000 cells/well) are incubated with either forskolin (10 nM—10 μM), GnRH (1 nM—1 μM) or GnRH-A (0.1 nM—100 nM) in a total volume of 100 μl on flashplates for 20 minutes at room temperature to assess for agonist activity. 100 μl of detection mix containing ^{125}I-cAMP is added to quench reactions according to the manufacturer's instructions. Plates are counted on a Packard TopCount after approximately two hours. Cyclic AMP levels are determined from standard curves generated to non-radioactive cAMP standards (10 nM-1 μM).

Data Analysis.

Cytosensor® Microphysiometer data are normalized utilizing Cytosoft® software (Molecular Devices, Sunnyvale, CA). EC_{50} values for agonists and IC_{50} values for inhibitors are generated utilizing Prism™ (version 2.01, GraphPad Software, San Diego, CA), a computer graphics and statistics program. Values for multiple experiments are presented as means ± SE of at least three replicate experiments.

Effect of Compounds on ^{125}I-GnRH-A Binding to GGH_3 Cells.

In order to assess the specific functionality, compounds were assessed for their ability to inhibit ^{125}I-GnRH-A binding to GGH_3 cells. The peptide ligands GnRH, GnRH-A, and Antide, but none of the tested compounds of the invention, blocked

^{125}I-GnRH-A binding to these cells. Thus, the compounds of the invention are GnRH antagonists.

Determination of Binding Inhibition Constants

Using the assay described below, K_i values for compounds of the invention were determined.

Chemicals and Reagents.

GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), was purchased from Bachem (Torrance, CA). Cell Culture media was purchased from Sigma (St. Louis, MO). Fetal bovine serum (FBS) was from Omega Scientific, Inc. (Tarzana, CA). G418 and penicillin/streptomycin were from Gemini (Calabasas, CA). Newborn calf serum was from Summit Biotech (Fort Collins, CO). All other reagents were of the highest quality from standard sources.

Cell Culture.

HEK 293 cells stably transfected with mouse or human GnRH receptors as described above were grown in Dulbecco's high-glucose, modified Eagle's medium (DMEM) supplemented with 0.2% G418, 10% fetal bovine serum (FBS) and 100U/mL penicillin/streptomycin. GH_3 cells stably transfected with the rat GnRH receptor (GGH_3) were provided by Dr. William Chin (Harvard Medical School, Boston, MA). These cells have been extensively characterized previously (Kaiser et al., 1997). The cells were grown in low glucose DMEM containing: 100U/mL penicillin/streptomycin, 0.6% G418 and 10% heat-inactivated FBS.

Cell Membrane Preparation.

HEK 293 cells containing mouse or human receptors, or rat pituitaries (Pel Freez Biologicals, Rogers, AR) were homogenized in buffer A containing: 50 mM Tris (pH 7.4), 0.32 M sucrose, 2 mM EGTA, 1 mM PMSF, 5 μg/ml aprotinen, 5 μg/ml Pepstatin A, and 1 μg/ml leupeptin. Homogenized cells were centrifuged at 4°C at 20,000 x *g* for 25 minutes, re-suspended in buffer A and re-centrifuged at 4°C at 20,000 x *g* for an additional 25 minutes. Total membrane protein was determined with a BCA kit (Pierce, Rockford, IL). Membranes were stored at -70°C at a final membrane protein concentration of approximately 5 mg/ml.

Radioligand Preparation.

The radioiodinated agonist analog of GnRH, [des-Gly^{10},D-Ala^{6}]GnRH ethylamide (^{125}I-GnRH-A), was used as the radioligand. One μg of GnRH-A diluted

in 0.5 M phosphate buffer (pH 7.4) was added to an Iodogen®-coated borosilicate glass tube (Pierce, Rockford, IL) containing 35 µl of 0.05 M phosphate buffer (pH 7.4-7.6) and 1 mCi of Na[^{125}I]. The reaction mixture was vortexed and incubated for 1 minute at room temperature. After one minute, the mixture was vortexed and allowed to incubate for an additional minute. 2 ml of 0.5 M acetic acid/1% BSA was added to the reaction tube and the mixture was added to a C18 Sep-Pak cartridge. The cartridge was washed with subsequent washes of 5 ml H_2O and 5 ml 0.5 M acetic acid and then eluted with 5 x 1 ml of 60%CH_3CN/40% 0.5 M acetic acid. The eluate was diluted with 3x volume of HPLC buffer A (0.1% TFA in H_2O) and loaded onto a C18 column. The iodinated product was eluted over 20-25 min with a gradient of 25-100% CH_3CN containing 0.1% TFA. The radioactive fractions (750 µl/fraction) were collected into clean polypropylene tubes containing 100 µl of 10% BSA. Fractions were assessed for biological activity by radiolig and binding. Specific activity of the radioligand was approximately 2200 Ci/mmol.

Radioligand Binding Assays.

Membranes were diluted to 0.01-0.5 mg/ml (depending upon the species of receptor) with assay buffer containing 50 mM HEPES (pH 7.4), 1 mM EDTA, 2.5 mM $MgCl_2$, and 0.1% BSA. Membranes (diluted to utilize similar receptor numbers between assays) were incubated with approximately 0.04-0.06 nM ^{125}I-GnRH-A in the presence or absence of competing agents (0.1 – 10,000 nM) in a total volume of 200 µl in 96-well polypropylene plates for 1 hour at room temperature. Assays were stopped by rapid filtration onto 96-well GF/C filters soaked in 0.1% polyethylenimine (PEI) utilizing a Packard 96-well cell harvester. Filters were washed three times with ice-cold PBS (50 mM $NaPO_4$, 0.9% NaCl, 2 mM $MgCl_2$, and 0.02% NaN_3, pH 7.4). 35 µl of scintillation cocktail was added to each filter well and filters were counted on a Packard Topcount. Control dose-response curves were generated to GnRH (0.1 nM-100 nM) in each competition binding experiment. Binding inhibition constants (K_i) for the GnRH agents were calculated and are provided in Table 2 below. K_i values were calculated from IC50 values according to Cheng et al., *Biochemical Pharmacol.* 22: 3099-3108, 1973.

$$K_i = \frac{IC_{50}}{1 + \frac{[\text{ligand}]}{K_d \text{ of ligand}}}$$

Table 2

K_i for GnRH Agents:

Inhibition Binding of ^{125}I-GnRH-A to GnRH Receptors of Various Species

Example No.	GnRH Receptor	K_i (nM)
A1	Human	>10000
	Mouse	ND
	Rat	ND
A2	Human	180
	Mouse	87
	Rat	69
A3	Human	42
	Mouse	16
	Rat	14
A4	Human	189
	Mouse	101
	Rat	84
A5	Human	42
	Mouse	134
	Rat	46
A6	Human	455
	Mouse	ND
	Rat	ND
A7	Human	244
	Mouse	435
	Rat	191
A8	Human	3
	Mouse	2
	Rat	4
A9	Human	2
	Mouse	3
	Rat	11
A10	Human	649

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	ND
A11	Human	460
	Mouse	ND
	Rat	ND
A12	Human	2716
	Mouse	ND
	Rat	ND
A13	Human	78
	Mouse	25
	Rat	80
A14	Human	844
	Mouse	ND
	Rat	ND
A15	Human	2
	Mouse	2
	Rat	2
A16	Human	475
	Mouse	ND
	Rat	ND
A17	Human	153
	Mouse	74
	Rat	126
B1	Human	0.42
	Mouse	1
	Rat	4
B2	Human	>1000
	Mouse	ND
	Rat	ND
B3	Human	3
	Mouse	2

Example No.	GnRH Receptor	K_i (nM)
	Rat	7
B4	Human	103
	Mouse	157
	Rat	563
B5	Human	14
	Mouse	ND
	Rat	14
B6	Human	999
	Mouse	ND
	Rat	ND
B7	Human	561
	Mouse	ND
	Rat	ND
B8	Human	>10000
	Mouse	ND
	Rat	ND
B9	Human	80
	Mouse	69
	Rat	203
B10	Human	4
	Mouse	6
	Rat	5
B11	Human	403
	Mouse	ND
	Rat	ND
B12	Human	520
	Mouse	ND
	Rat	ND
B13	Human	>10000
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
B14	Human	5
	Mouse	29
	Rat	32
B15	Human	11
	Mouse	7
	Rat	10
B16	Human	2
	Mouse	2
	Rat	4
B17	Human	251
	Mouse	ND
	Rat	ND
B18	Human	6
	Mouse	3
	Rat	4
B19	Human	138
	Mouse	84
	Rat	72
B20	Human	4906
	Mouse	ND
	Rat	ND
B21	Human	14
	Mouse	11
	Rat	24
B22	Human	16
	Mouse	20
	Rat	42
B23	Human	5
	Mouse	6
	Rat	13
B24	Human	457

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	ND
B25	Human	1180
	Mouse	ND
	Rat	ND
B26	Human	1.4
	Mouse	1.1
	Rat	1.7
B27	Human	0.9
	Mouse	ND
	Rat	0.7
B28	Human	4
	Mouse	ND
	Rat	1
B29	Human	1
	Mouse	ND
	Rat	0.69
B30	Human	2
	Mouse	1.2
	Rat	1
B31	Human	2
	Mouse	0.74
	Rat	1
B32	Human	2
	Mouse	2
	Rat	5
B33	Human	6
	Mouse	7
	Rat	9
B34	Human	0.2
	Mouse	ND

Example No.	GnRH Receptor	K_i (nM)
	Rat	0.3
B35	Human	3
	Mouse	6
	Rat	3
B36	Human	0.18
	Mouse	0.26
	Rat	0.43
B37	Human	5
	Mouse	4
	Rat	4
B38	Human	7
	Mouse	6
	Rat	9
B39	Human	2
	Mouse	2
	Rat	3
B40	Human	0.2
	Mouse	ND
	Rat	0.4
B41	Human	ND
	Mouse	ND
	Rat	ND
B42	Human	31
	Mouse	21
	Rat	96
B43	Human	63
	Mouse	411
	Rat	711
B44	Human	1362
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
B45	Human	1
	Mouse	0.96
	Rat	2
B46	Human	0.5
	Mouse	ND
	Rat	0.6
B47	Human	1402
	Mouse	ND
	Rat	ND
B48	Human	11
	Mouse	ND
	Rat	15
B49	Human	4
	Mouse	4
	Rat	16
B50	Human	1
	Mouse	3
	Rat	2
B51	Human	3
	Mouse	0.13
	Rat	6
B52	Human	0.1
	Mouse	0.18
	Rat	0.13
B53	Human	10
	Mouse	ND
	Rat	8
B54	Human	13
	Mouse	ND
	Rat	7
B55	Human	2

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	3
B56	Human	2
	Mouse	ND
	Rat	3
B57	Human	0.96
	Mouse	ND
	Rat	0.24
B58	Human	2
	Mouse	0.93
	Rat	2
B59	Human	3
	Mouse	6.4
	Rat	2
B60	Human	0.67
	Mouse	2
	Rat	0.8
B61	Human	3
	Mouse	ND
	Rat	0.34
B62	Human	0.58
	Mouse	0.8
	Rat	0.7
B63	Human	3
	Mouse	2
	Rat	3
B64	Human	25
	Mouse	21
	Rat	29
B65	Human	0.41
	Mouse	0.4

Example No.	GnRH Receptor	K_i (nM)
	Rat	0.33
B66	Human	3
	Mouse	2
	Rat	5
B67	Human	350
	Mouse	ND
	Rat	ND
B68	Human	0.86
	Mouse	1
	Rat	1
B69	Human	5
	Mouse	3
	Rat	7
B70	Human	11
	Mouse	ND
	Rat	13
B71	Human	11
	Mouse	ND
	Rat	38
B72	Human	5
	Mouse	3
	Rat	5
B73	Human	2
	Mouse	ND
	Rat	1
B74	Human	2117
	Mouse	ND
	Rat	ND
B75	Human	3096
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
B76	Human	1909
	Mouse	ND
	Rat	ND
B77	Human	16
	Mouse	30
	Rat	34
B78	Human	1010
	Mouse	ND
	Rat	ND
B79	Human	29
	Mouse	7
	Rat	33
B80	Human	ND
	Mouse	ND
	Rat	ND
B81	Human	9
	Mouse	2
	Rat	4
B82	Human	29
	Mouse	25
	Rat	34
B83	Human	5
	Mouse	10
	Rat	13
B84	Human	10
	Mouse	6
	Rat	5
B85	Human	1401
	Mouse	ND
	Rat	ND
B86	Human	196

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	ND
B87	Human	580
	Mouse	ND
	Rat	ND
B88	Human	4
	Mouse	ND
	Rat	6
B89	Human	0.24
	Mouse	0.22
	Rat	0.14
B90	Human	0.42
	Mouse	ND
	Rat	0.52
B91	Human	0.42
	Mouse	0.97
	Rat	0.71
B92	Human	0.96
	Mouse	2
	Rat	3
B93	Human	24
	Mouse	51
	Rat	39
B94	Human	102
	Mouse	75
	Rat	154
B95	Human	>10000
	Mouse	ND
	Rat	ND
B96	Human	987
	Mouse	ND

Example No.	GnRH Receptor	K_i (nM)
	Rat	ND
B97	Human	53
	Mouse	18
	Rat	65
B98	Human	2751
	Mouse	ND
	Rat	ND
B99	Human	1268
	Mouse	ND
	Rat	ND
B100	Human	261
	Mouse	22
	Rat	26
B101	Human	11
	Mouse	4
	Rat	3
B102	Human	372
	Mouse	ND
	Rat	ND
B103	Human	ND
	Mouse	ND
	Rat	ND
B104	Human	2
	Mouse	3
	Rat	4
B105	Human	1533
	Mouse	ND
	Rat	ND
B106	Human	478
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
B107	Human	94
	Mouse	43
	Rat	41
B108	Human	>10000
	Mouse	ND
	Rat	ND
B109	Human	2804
	Mouse	ND
	Rat	ND
B110	Human	1
	Mouse	0.8
	Rat	1
B111	Human	55
	Mouse	13
	Rat	16
B112	Human	5
	Mouse	ND
	Rat	3
B113	Human	703
	Mouse	ND
	Rat	ND
B114	Human	7
	Mouse	ND
	Rat	5
B115	Human	ND
	Mouse	ND
	Rat	ND
B116	Human	0.84
	Mouse	ND
	Rat	0.67
B117	Human	6

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	2
B118	Human	0.57
	Mouse	ND
	Rat	1.1
B119	Human	3
	Mouse	ND
	Rat	3
B120	Human	0.5
	Mouse	ND
	Rat	1
B121	Human	2
	Mouse	ND
	Rat	0.73
B122	Human	1
	Mouse	ND
	Rat	0.57
B123	Human	6.6
	Mouse	ND
	Rat	4
B124	Human	1
	Mouse	ND
	Rat	0.57
B125	Human	1
	Mouse	ND
	Rat	0.49
B126	Human	0.72
	Mouse	ND
	Rat	0.53
B127	Human	0.92
	Mouse	ND

Example No.	GnRH Receptor	K_i (nM)
	Rat	0.47
B128	Human	0.56
	Mouse	ND
	Rat	0.23
B129	Human	0.70
	Mouse	ND
	Rat	0.62
B130	Human	5
	Mouse	ND
	Rat	4
B131	Human	1
	Mouse	ND
	Rat	2
B132	Human	0.37
	Mouse	ND
	Rat	0.47
B133	Human	4
	Mouse	ND
	Rat	4
B134	Human	0.79
	Mouse	ND
	Rat	0.5
B135	Human	1
	Mouse	ND
	Rat	1
B136	Human	0.21
	Mouse	0.35
	Rat	0.6
B137	Human	0.7
	Mouse	ND
	Rat	0.22

Example No.	GnRH Receptor	K_i (nM)
B138	Human	4.7
	Mouse	ND
	Rat	3.7
B139	Human	9.2
	Mouse	ND
	Rat	ND
B140	Human	0.66
	Mouse	0.35
	Rat	0.25
B141	Human	>1000
	Mouse	ND
	Rat	ND
B142	Human	73
	Mouse	ND
	Rat	32
B143	Human	10
	Mouse	ND
	Rat	21
B144	Human	3093
	Mouse	ND
	Rat	ND
B145	Human	650
	Mouse	ND
	Rat	ND
B146	Human	28
	Mouse	ND
	Rat	18
B147	Human	3
	Mouse	ND
	Rat	3
B148	Human	27

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	ND
B149	Human	198
	Mouse	ND
	Rat	ND
B150	Human	13
	Mouse	14
	Rat	11
B151	Human	ND
	Mouse	ND
	Rat	ND
B152	Human	21
	Mouse	ND
	Rat	170
B153	Human	4.9
	Mouse	ND
	Rat	2
B154	Human	ND
	Mouse	ND
	Rat	ND
B155	Human	ND
	Mouse	ND
	Rat	ND
C1	Human	2
	Mouse	1
	Rat	4
C2	Human	7
	Mouse	4
	Rat	4
C3	Human	3669
	Mouse	ND

Example No.	GnRH Receptor	K_i (nM)
	Rat	ND
C4	Human	25
	Mouse	51
	Rat	76
C5	Human	17
	Mouse	11
	Rat	27
C6	Human	>10000
	Mouse	ND
	Rat	ND
C7	Human	12
	Mouse	26
	Rat	51
C8	Human	51
	Mouse	31
	Rat	38
C9	Human	>10000
	Mouse	ND
	Rat	ND
C10	Human	1
	Mouse	1
	Rat	2
C11	Human	220
	Mouse	154
	Rat	198
C12	Human	12
	Mouse	3
	Rat	11
C13	Human	15
	Mouse	5
	Rat	17

Example No.	GnRH Receptor	K_i (nM)
C14	Human	693
	Mouse	ND
	Rat	ND
C15	Human	11
	Mouse	5
	Rat	15
C16	Human	450
	Mouse	ND
	Rat	ND
C17	Human	14
	Mouse	75
	Rat	154
C18	Human	5
	Mouse	5
	Rat	7
C19	Human	59
	Mouse	36
	Rat	16
C20	Human	10
	Mouse	29
	Rat	15
C21	Human	29
	Mouse	13
	Rat	11
C22	Human	74
	Mouse	97
	Rat	142
C23	Human	4
	Mouse	3
	Rat	0.34
D1	Human	>10000

Example No.	GnRH Receptor	K_i (nM)
	Mouse	ND
	Rat	ND
D2	Human	841
	Mouse	ND
	Rat	ND
D3	Human	3747
	Mouse	ND
	Rat	ND
F1	Human	31
	Mouse	36
	Rat	65
F2	Human	6430
	Mouse	ND
	Rat	ND
F3	Human	380
	Mouse	ND
	Rat	ND
H1	Human	27
	Mouse	14
	Rat	115
H2	Human	7
	Mouse	20
	Rat	207
I1	Human	>10000
	Mouse	ND
	Rat	ND
I2	Human	6540
	Mouse	ND
	Rat	ND
I3	Human	4910
	Mouse	ND

Example No.	GnRH Receptor	K_i (nM)
	Rat	ND
I4	Human	8
	Mouse	8
	Rat	6
I5	Human	455
	Mouse	ND
	Rat	ND
I6	Human	>10000
	Mouse	ND
	Rat	ND
I7	Human	3654
	Mouse	ND
	Rat	ND
I8	Human	7379
	Mouse	ND
	Rat	ND
I9	Human	>10000
	Mouse	ND
	Rat	ND
I10	Human	>10000
	Mouse	ND
	Rat	ND
I11	Human	3226
	Mouse	ND
	Rat	ND
I12	Human	>10000
	Mouse	ND
	Rat	ND
I13	Human	>10000
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
I14	Human	2474
	Mouse	ND
	Rat	ND
I15	Human	2740
	Mouse	ND
	Rat	ND
I16	Human	2204
	Mouse	ND
	Rat	ND
I17	Human	>10000
	Mouse	ND
	Rat	ND
I18	Human	>10000
	Mouse	ND
	Rat	ND
I19	Human	8006
	Mouse	ND
	Rat	ND
I20	Human	>10000
	Mouse	ND
	Rat	ND
I21	Human	>10000
	Mouse	ND
	Rat	ND
I22	Human	>10000
	Mouse	ND
	Rat	ND
I23	Human	1313
	Mouse	ND
	Rat	ND
I24	Human	88

Example No.	GnRH Receptor	K_i (nM)
	Mouse	64
	Rat	76
I25	Human	992
	Mouse	ND
	Rat	ND
I26	Human	113
	Mouse	67
	Rat	93
I28	Human	12361
	Mouse	ND
	Rat	ND
I29	Human	3201
	Mouse	ND
	Rat	ND
I30	Human	>10000
	Mouse	ND
	Rat	ND
I31	Human	>10000
	Mouse	ND
	Rat	ND
I32	Human	3700
	Mouse	ND
	Rat	ND
I33	Human	8400
	Mouse	ND
	Rat	ND
I34	Human	99
	Mouse	24
	Rat	61
I35	Human	44
	Mouse	16

Example No.	GnRH Receptor	K_i (nM)
	Rat	29
I36	Human	6
	Mouse	9
	Rat	9
I37	Human	13
	Mouse	6
	Rat	10
I38	Human	6
	Mouse	4
	Rat	9
I39	Human	ND
	Mouse	ND
	Rat	ND
I40	Human	ND
	Mouse	ND
	Rat	ND
I41	Human	ND
	Mouse	ND
	Rat	ND
I42	Human	6870
	Mouse	ND
	Rat	ND
I43	Human	>1000
	Mouse	ND
	Rat	ND
I44	Human	>1000
	Mouse	ND
	Rat	ND
J1	Human	>1000
	Mouse	ND
	Rat	ND

Example No.	GnRH Receptor	K_i (nM)
J2	Human	>1000
	Mouse	ND
	Rat	ND
J3	Human	>1000
	Mouse	ND
	Rat	ND
J4	Human	>1000
	Mouse	ND
	Rat	ND
K1	Human	1620
	Mouse	ND
	Rat	ND

ND = not determined

Microphysiometry.

GGH_3 cells were seeded in low-buffered minimal essential media (MEM, Sigma) containing 25 mM NaCl and 0.1% BSA at a density of 500,000 cells/capsule onto the polycarbonate membrane (3 μm porosity) of cell capsule cups (Molecular Devices, Sunnyvale, CA). Capsule cups were transferred to sensor chambers where cells were held in close apposition to a silicon sensor within a sensor chamber, which measures small changes in pH in the microvolume of the sensor chamber. Low-buffered medium was pumped continuously across the cells at a rate of approximately 100 ul/min from one of two fluid reservoirs. A selection valve determined which reservoir from which fluid was perifused onto the cells.

The Cytosensor®Microphysiometer generates a voltage signal, which is a linear function of pH, every second. In order to measure acidification rates, flow to the sensor chamber containing the cells was periodically interrupted, allowing for excreted acidic metabolites to build up in the extracellular fluid of the cells. In these experiments, cells were maintained at 37 °C on a two-minute flow cycle with cells being perfused with media for 80 seconds followed by 40 seconds in which the flow of media was stopped. During this 40-second interval, acidification rates were measured for a 30-second interval. In this fashion, a single acidification rate was

calculated every two minutes. The Cytosensor® Microphysiometer unit contains eight such sensor units, allowing for eight simultaneous experiments to be performed. Each unit was individually programmed utilizing a computer linked to the system.

GGH_3 cells were initially equilibrated in the low-buffered MEM media for a period of 30-60 minutes in which basal acidification rates (measured as uV/sec), in the absence of any stimuli, were monitored. When the basal rate of acidification changed by less than ten percent over a period of twenty minutes, experiments were initiated. Cells were pretreated for 20 minutes with cell media containing vehicle (1% DMSO) or test compounds at various concentrations (in 1% DMSO final concentration) prior to stimulation with GnRH at various concentrations.

Total Inositol Phosphates Measurement.

Approximately 200,000 GGH_3 cells or 293 cells containing human GnRH receptors were plated onto 24-well tissue culture plates using DMEM media. The following day, cells were loaded with [^{3}H] myoinositol (0.5 Ci/ml) for 16-18 hours in inositol-free medium. The medium was aspirated and the cells rinsed with serum-free DMEM. Cells were pretreated with various compounds (dissolved in 1% DMSO final concentration) for 30 minutes and were then stimulated for 45 minutes with GnRH (0.1 nM—1 μM) dissolved in DMEM media in a total volume of 1 mL containing 10 mM LiCl at 37°C. The media was replaced with 1 mL ice-cold 10 mM formic acid, which stopped the reaction and also served to extract cellular lipids. Inositol phosphates were separated by ion-exchange chromatography on Dowex columns, which were washed with 2.5 mL of 10 mM myoinositol and 10 mM formic acid. The columns were then washed with 5 mL of 60 mM sodium formate and 5 mM borax, and total inositol phosphates were eluted with 5 mL of 1 M ammonium formate, 0.1 M formic acid. The column eluates were added to liquid scintillation vials containing 15 ml of scintillation cocktail and were counted by liquid scintillation counting.

Pharmacokinetics and Metabolism:

Pharmacokinetics.

Rats (male or female, 200-225 g) were prepared with indwelling jugular vein cannula as described by Harms et al., *Applied Physiol.* 36:391-398 (1974), and allowed to recover overnight with free access to the standard vivarium chow and water. The compounds were administered to female rats at 5 mg/kg i.v. and 10 mg/kg

p.o. as solutions in 10% DMSO+10% cremophor+80% saline or 10% cremophor+90% saline. The male rats were dosed orally at 50 mg/kg in the vehicles specified in Table 3. The blood samples were withdrawn at specific times, plasma was immediately separated and compound extracted with ethyl acetate. The samples were analyzed by LC-MS using 30-90% gradient of ACN in 50 mM ammonium acetate.

The pharmacokinetic parameters were calculated using WinNonlin software (Scientific Consulting Inc.). The bioavailability was calculated as AUCp.o./AUCi.v., where AUCp.o. and AUC i.v. are areas under the plasma concentration-time curve after oral and i.v. administration, respectively.

In vitro metabolism.

Human, rat, dog, and monkey liver microsomes were isolated by differential centrifugation. Specimens of human liver were obtained from the International Institute for the Advancement of Medicine (Scranton, PA). The disappearance of the parent compound was studied in a mixture containing 5 uM compound, 0.5 mg/ml microsomal protein, and 2 mM NADPH in 50 mM K Phosphate buffer, pH 7.4. Samples were incubated for 30 minutes at 37^0C. The reaction was terminated by the addition of acetonitrile and compounds analyzed by LC-MS as described above.

Table 3

Compound No.	Human		Male Rat						Female Rat						Rat	Dog	Monkey	HSA	Solubility	
	% rem.		% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	plasma	% rem.	% rem.	column	µg/ml	
	5'	30'	5'	30'	hr	µM	hr		5'	30'	hr	µM	hr		% remain	30'	30'	α	pH2	pH6.5
A10	ND	45	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
A2	ND	40		ND	ND	ND	ND	ND	ND	28	0.6	3.34	0.5	23% [1]	ND	ND	ND	ND	ND	ND
A3	ND	51	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
A4	ND	55	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
A6	ND	35	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
A8	ND	30	ND	ND	ND	ND	ND	ND	ND	68	2.1	1	1	7% [2]	76	0	ND	>30	ND	0.3
A9	ND	36	ND	ND	ND	ND	ND	ND	ND	86	2	0.2	0.5	4% [1]	9	ND	ND	18	ND	0.7
B1	ND	50	70	16	ND	0.3	1	ND	ND	89	3.2	1.7	1	41% [1]	79	8	1	12	ND	0.9
B10	ND	23	ND	ND	ND	ND	ND	ND	ND	78	ND	ND	ND	ND	100	0	ND	3	ND	1.9
B11	ND	24	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B12	ND	35	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B13	ND	42	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B14	ND	30	ND	ND	ND	ND	ND	ND	ND	57	4	ND	ND	**	1	1	ND	2	ND	3.5
B15	ND	58	ND	ND	ND	ND	ND	ND	ND	45	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B3	ND	24	ND	1	2.8	1	1	15% [1]	ND	38	2.9	4	3	74% [1]	100	1	0	11	ND	0.8
B4	ND	50	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B7	ND	60	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B74	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B75	ND	80	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B76	ND	76	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B77	ND	46	ND	ND	ND	ND	ND	ND	ND	43	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B79	ND	57	ND	ND	ND	ND	ND	ND	ND	74	2	1	1	10% [2]	ND	ND	ND	ND	ND	ND
B9	ND	78	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
C10	ND	32	ND	ND	ND	ND	ND	ND	ND	74	ND	ND	ND	ND	92	ND	ND	15	ND	0.7
C18	ND	57	63	7	ND	1.5	1	ND	ND	88	1.7	1	1	21% [2]	82	4	ND	>30	ND	0.5
C23	88	42	55	15	2.5	0.4	1	17% [2]	95	87	1.6	1.5	1	33% [2]	76	0	ND	26	ND	5.9
C4	ND	85	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	ND
C7	ND	16	ND	ND	ND	ND	ND	ND	ND	34	ND	ND	ND	ND	100	5	ND	ND	ND	0.4
C8	ND	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
C9	ND	43	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
D3	ND	49	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H1	ND	86	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H2	ND	100	ND	ND	ND	ND	ND	ND	ND	ND	1.5	0.1	1	0.1% [1]	100	ND	ND	ND	ND	0.4

Compound No.	Human	Male Rat					Female Rat					Rat	Dog	Monkey	HSA	Solubility
	% rem.	% rem.	$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	% rem.	$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	plasma	% rem.	% rem.	column	µg/ml

	5'	30'	5'	30'	hr	µM	hr		5'	30'	hr	µM	hr		% remain	30'	30'	α	pH2	pH6.5
B101	ND	39	ND	3	ND	ND	ND	ND	ND	60	1.8	1.2	0.5	29%[1]	100	1	1	2	ND	ND
B104	ND	37	ND	11	ND	ND	ND	ND	ND	69	ND	ND	ND	ND	ND	45	1	3	5.8	4.4
B140	ND	49	ND	1	ND	ND	ND	ND	ND	87	1.1	0.4	1	7%[12]	ND	2	1	22	0.7	0.7
B16	ND	60	80	7	ND	ND	ND	ND	ND	86	2.5	2.3	2	37%[13]	84	10	3	>30	1.2	0.4
B18	ND	72	72	13	ND	ND	ND	ND	ND	86	2.6	2	2	17%[13]	88	11	1	>30	ND	0.8
B21	ND	93	ND	31	ND	ND	ND	ND	ND	84	2.5	2.4	1	8%[1]	100	25	7	>30	ND	ND
B22	ND	58	ND	11	ND	ND	ND	ND	ND	94	1.7	1.8	1	19%[1]	15	32	1	>30	ND	ND
B30	ND	75	ND	ND	ND	ND	ND	ND	ND	95	3.2	0.5	0.5	35%[1]	100	45	0	6	ND	1.4
B31	ND	85	73	18	ND	0.5	1	ND	ND	92	3.4	0.9	1	34%[1]	100	36	2	5	ND	0.7
B32	ND	31	ND	0	ND	ND	ND	ND	ND	74	1.6	0.3	0.25	8%[1]	7	1	1	15	0.9	1.4
B33	ND	73	ND	1	ND	ND	ND	ND	ND	82	ND	ND	ND	ND	42	3	1	23	ND	0.8
B35	ND	67	64	32	ND	1.1	2	ND	ND	87	5.3	0.9	3	31%[11]	100	63	2	7	ND	1
B36	ND	67	66	19	1.1	0.2	1	8%[8]	ND	76	2.2	1.4	0.5	27%[1]	100	43	1	6	ND	1
B37	ND	65	60	12	ND	1.2	2	ND	ND	87	2.5	1.8	2	52%[13]	100	17	0	37	ND	0.5
B38	ND	51	ND	31	ND	4.5	2	ND	ND	74	3.8	3.7	2	46%[1]	100	45	3	26	ND	0.9
B39	ND	60	ND	1	ND	1.3	3	ND	ND	100	2.5	0.8	2	17%[13]	100	14	1	>30	ND	0.7
B62	ND	28	ND	8	1.3	<0.03	ND	<1%[1]	ND	83	1.7	1.4	1	24%[10]	100	2	2	14	ND	0.4
B63	ND	76	61	13	ND	ND	ND	ND	ND	85	2.8	0.7	1	32%[14]	100	74	11	4	ND	2.8
B65	ND	62	ND	ND	ND	ND	ND	ND	ND	89	2.4	0.35	1	50%[1]	100	6	1	10	ND	0.9
B66	ND	70	80	21	ND	ND	ND	ND	ND	80	2.8	0.8	2	35%[14]	100	18	3	25	ND	0.8
B68	ND	41	ND	4	ND	ND	ND	ND	ND	70	2.3	0.6	2	15%[21]	1	10	0	6	7.2	2.2
B72	ND	83	ND	0	ND	ND	ND	ND	ND	49	3.4	1.1	2	65%[21]	100	43	0	3	ND	1.8
B81	ND	90	ND	12	ND	ND	ND	ND	ND	81	2.7	2.7	1	57%[1]	100	20	1	14	ND	0.8
B83	ND	37	ND	1	ND	ND	ND	ND	ND	82	3.6	0.3	1	5%[1]	100	4	1	13	ND	0.8
B84	ND	60	ND	13	ND	0.1	1	ND	ND	86	1.7	0.6	1	47%[14]	100	18	2	5	ND	2.1
B91	ND	62	ND	11	ND	ND	ND	ND	ND	79	1.9	0.9	1	14%[10]	100	2	5	8	0.3	0.4
B92	ND	58	ND	3	ND	ND	ND	ND	ND	68	1.1	0.7	1	10%[2]	21	18	1	>30	ND	ND
C12	ND	55	ND	13	ND	ND	ND	ND	ND	59	3.5	4.6	0.5	34%[1]	ND	20	0	3	7	ND
C13	ND	63	ND	3	ND	ND	ND	ND	ND	50	ND	ND	ND	ND	46	ND	ND	8	0.3	ND
C14	ND	82	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
C17	ND	64	79	21	4.1	0.4	1	15%[1]	ND	77	2.9	4.4	1	75%[1]	80	47	1	2	0.9	1.5
C2	ND	80	77	30	ND	3.2	2	ND	ND	85	2.9	1.7	1	57%[1]	24	65	2	5	ND	0.7
C5	ND	86	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	25	ND	ND

Table 3 (cont'd.)

Compound No.	Human		Male Rat						Female Rat						Rat	Dog	Monkey	HSA	Solubility	
	% rem.		% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	plasma	% rem.	% rem.	column	µg/ml	
	5'	30'	5'	30'	hr	µM	hr		5'	30'	hr	µM	hr		% remain	30'	30'	α	pH2	pH6.5
B34	ND	83	ND	10	ND	ND	ND	ND	ND	30	ND	ND	ND	ND	ND	8	18	ND	ND	ND
B40	ND	85	ND	72	ND	ND	ND	ND	ND	83	ND	ND	ND	ND	ND	68	47	ND	ND	ND
B46	ND	85	ND	62	ND	ND	ND	ND	ND	75	ND	ND	ND	ND	ND	76	57	ND	ND	ND
B82	ND	82	ND	71	ND	ND	ND	ND	ND	76	ND	ND	ND	ND	ND	80	56	ND	ND	ND
B53	ND	81	ND	13	ND	ND	ND	ND	ND	50	ND	ND	ND	ND	ND	8	26	ND	ND	ND
A15	ND	52	ND	3	ND	ND	ND	ND	ND	82	ND	ND	ND	ND	ND	1	0	12	ND	0.6
B114	ND	51	ND	25	ND	ND	ND	ND	ND	82	ND	ND	ND	ND	ND	22	0	ND	ND	1.5
B143	ND	69	ND	17	ND	ND	ND	ND	ND	70	ND	ND	ND	ND	ND	11	4	4	ND	0.3
B147	ND	57	ND	19	ND	ND	ND	ND	ND	89	ND	ND	ND	ND	ND	35	11	ND	ND	0.4
B41	ND	57	ND	29	ND	3.6	1	ND	ND	79	3.6	4	2	64%[1]	ND	58	1	8	ND	1
B45	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.5
B49	ND	59	ND	61	ND	ND	ND	ND	ND	95	2.6	2.3	1	17%[1]	83	63	0	>30	ND	0.5
B50	ND	50	ND	70	ND	ND	ND	ND	ND	82	2.2	5	2	15%[1]	100	77	0	>30	ND	0.5
B51	ND	86	ND	2	ND	ND	ND	ND	ND	50	2.3	0.2	1	4%[1]	94	27	1	7	ND	0.6
B52	ND	57	ND	43	ND	0.9	3	ND	ND	90	6.6	0.4	2	27%[1]	100	33	0	4	ND	8
B54	ND	38	ND	1	ND	ND	ND	ND	ND	77	ND	ND	ND	ND	ND	25	2	ND	ND	0.5
B55	ND	75	ND	20	ND	ND	ND	ND	ND	60	ND	ND	ND	ND	ND	12	30	>10	ND	4.2
B56	ND	57	ND	54	ND	ND	ND	ND	ND	88	ND	ND	ND	ND	ND	31	0	>20	ND	2.8
B57	ND	76	ND	24	ND	4.8	7	ND	ND	61	>10	1.2	5	46%[1]	100	33	48	>20	ND	>15
B58	ND	63	ND	40	ND	ND	ND	ND	ND	91	ND	ND	ND	ND	ND	18	0	21	ND	1
B59	ND	38	ND	1	ND	ND	ND	ND	ND	73	ND	ND	ND	ND	ND	2	0	18	ND	ND
B60	ND	55	ND	4	ND	ND	ND	ND	ND	80	ND	ND	ND	ND	ND	3	0	16	ND	ND
B61	ND	86	ND	15	ND	2.3	7	ND	ND	43	6.2	0.7	5	34%[1]	100	13	54	5	ND	12
B64	ND	69	ND	0	ND	ND	ND	ND	ND	71	ND	ND	ND	ND	ND	0	0	0.9	ND	7
B69	ND	80	ND	6	ND	ND	ND	ND	ND	100	2.4	5.2	1	53%[1]	ND	75	1	4	ND	2.5
B70	ND	61	ND	8	ND	ND	ND	ND	ND	82	ND	ND	ND	ND	ND	31	0	5	ND	1
B71	ND	72	ND	23	ND	ND	ND	ND	ND	76	ND	ND	ND	ND	ND	25	7	>10	ND	0.4
B73	ND	82	ND	4	ND	ND	ND	ND	ND	20	ND	ND	ND	ND	ND	26	14	28	ND	14
B88	ND	74	ND	46	ND	ND	ND	ND	ND	81	ND	ND	ND	ND	ND	54	20	14	ND	0.4
C15	ND	59	ND	16	ND	3.2	3	ND	ND	89	2	1.7	0.5	31%[1]	ND	52	0	2	ND	ND
C20	ND	28	ND	0	ND	ND	ND	ND	ND	17	1	<0.1	ND	<1%[1]	0	1	1	5	ND	4.5
C22	ND	5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
I26	ND	44	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
I36	ND	26	ND	0	ND	ND	ND	ND	ND	82	3.2	0.4	0.5	20%[1]	100	0	0	3	ND	4
I37	ND	66	ND	ND	ND	ND	ND	ND	ND	89	3.4	0.7	1	25%[1]	ND	ND	ND	21	ND	0.8
I38	ND	82	ND	17	ND	ND	ND	ND	ND	82	2.1	0.9	2	20%[1]	24	7	2	8	ND	1
I4	ND	68	ND	31	ND	ND	ND	ND	ND	89	3.1	0.7	2	21%[1]	81	30	1	10	ND	0.2

Table 3 (cont'd.)

Compound No.	Human		Male Rat						Female Rat						Rat	Dog	Monkey	HSA	Solubility	
	% rem.		% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	% rem.		$T_{1/2}$	C_{max}	T_{max}	$F_{p.o.}$	plasma	% rem.	% rem.	column	µg/ml	
	5'	30'	5'	30'	hr	µM	hr		5'	30'	hr	µM	hr		% remain	30'	30'	α	pH2	pH6.5
B112	ND	73	ND	11	ND	ND	ND	ND	ND	51	ND	ND	ND	ND	ND	15	18	ND	ND	ND
B116	ND	78	ND	63	ND	ND	ND	ND	ND	100	ND	ND	ND	ND	100	33	0	>30	ND	1.6
B117	ND	56	ND	9	ND	ND	ND	ND	ND	59	ND	ND	ND	ND	ND	5	0	2	ND	>15
B118	ND	60	ND	31	ND	ND	ND	ND	ND	84	5.9	0.3	3	8%[1]	100	15	1	>4	ND	3.8
B119	ND	72	ND	80	ND	ND	ND	ND	ND	96	2.9	1.2	1	11%[1]	95	82	ND	>30	ND	0.5
B120	ND	51	ND	13	ND	ND	ND	ND	ND	57	1.8	1	1	23%[1]	100	12	1	>4	ND	10
B121	ND	71	ND	29	ND	ND	ND	ND	ND	64	5.2	0.9	7	45%[1]	86	36	1	>30	ND	9
B122	ND	45	ND	50	ND	ND	ND	ND	ND	84	ND	ND	ND	ND	ND	32	0	ND	ND	ND
B123	ND	12	ND	0	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	ND	4	0	ND	ND	ND
B124	ND	95	ND	76	ND	ND	ND	ND	ND	77	4.6	0.9	3	35%[1]	ND	65	59	5	ND	ND
B125	ND	68	ND	33	ND	ND	ND	ND	ND	77	ND	ND	ND	ND	ND	23	1	ND	ND	ND
B126	ND	92	ND	15	ND	ND	ND	ND	ND	53	ND	ND	ND	ND	ND	12	30	ND	ND	ND
B127	ND	86	ND	15	ND	ND	ND	ND	ND	50	ND	ND	ND	ND	ND	12	25	ND	ND	ND
B128	ND	43	ND	21	ND	ND	ND	ND	ND	78	ND	ND	ND	ND	ND	1	0	ND	ND	ND
B129	ND	47	ND	12	ND	ND	ND	ND	ND	84	ND	ND	ND	ND	ND	2	0	ND	ND	ND
B130	ND	97	ND	48	ND	ND	ND	ND	ND	70	ND	ND	ND	ND	ND	45	78	ND	ND	ND
B131	ND	95	ND	87	ND	ND	ND	ND	ND	91	ND	ND	ND	ND	ND	51	53	ND	ND	ND
B132	ND	86	ND	83	ND	ND	ND	ND	ND	86	7.9	0.6	3	31%[1]	ND	58	51	7	ND	ND
B133	ND	90	ND	35	ND	ND	ND	ND	ND	91	ND	ND	ND	ND	ND	72	73	ND	ND	ND
B136	ND	82	ND	48	ND	ND	ND	ND	ND	55	ND	ND	ND	ND	ND	51	54	ND	ND	ND
B28	ND	53	ND	24	ND	ND	ND	ND	ND	85	ND	ND	ND	ND	ND	25	1	ND	ND	ND
B29	ND	27	ND	49	ND	ND	ND	ND	ND	85	ND	ND	ND	ND	ND	35	0	ND	ND	ND
B89	ND	99	ND	40	ND	2.6	5	ND	ND	78	8.9	0.7	7	31%[1]	100	44	55	>10	ND	50
B90	ND	91	ND	65	ND	ND	ND	ND	ND	80	ND	ND	ND	ND	ND	70	44	ND	ND	ND

Table 3 Notes:

[1] 10 mg/kg as 5 mg/ml solution in 10% DMSO 10% cremophor 80% saline

[2] 10 mg/kg as 5 mg/ml solution in 10% cremophor 90% saline

[3] 50mg/kg as 25mg/ml solution in 50%Labrasol50%H2O(Cmax-1.4uM,Tmax-1hras100mg/ml inLabrasol;Cmax<0.05uMas25mg/ml in0.5%CMC)

[4] 50 mg/kg as 25 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.04uM, Tmax - 2hr as 25 mg/ml in 0.5%CMC)

[5] 50 mg/kg as 50 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.6uM, Tmax - 1hr as 100 mg/ml in PEG400; Cmax - 0.6uM, Tmax - 5hr as 100mg/ml in PG; Cmax - 0.3uM Tmax - 3hr as 25 mg/ml in 0.5%CMC)

[6] 50 mg/kg as 25 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.1uM, Tmax - 1hr as 100mg/ml in Labrasol; Cmax<0.1uM as 100mg/ml in PEG400 or 25 mg/ml in 0.5%CMC)

[7] 50 mg/kg as 25 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.2uM, Tmax - 5hr as 100 mg/ml in PEG400; Cmax - 0.4uM, Tmax - 5hr as 25 mg/ml solution in 0.5%CMC)

[8] 20 mg/kg as 10 mg/ml solution in 50% Labrasol 50% H2O (at 50mg/kg dose: Cmax -0.1uM Tmax - 2hr as 25 mg/ml in 50%Labrasol 50%H2O; Cmax<0.05uM as 100mg/ml in PEG400 or 25 mg/ml in 0.5%CMC)

[9] 20 mg/kg as 10 mg/ml solution in 10% DMSO 10% cremophor 80% saline (when given as 40 mg/ml in PEG400 or PG, $F_{p.o.}$ was 0%)

[10] 10 mg/kg as 5 mg/ml solution in 10% DMSO 20% cremophor 70% saline

[11] 6 mg/kg as 3 mg/ml solution in 10% DMSO 10% cremophor 80% saline

[12] 10 mg/kg as 5 mg/ml solution in 30% Labrasol 70% saline

[13] 10 mg/kg as 5 mg/ml solution in 50% Labrasol 50% H2O

[14] 5 mg/kg as 2.5 mg/ml solution in 10% DMSO 10% cremophor 80% saline

[15] 50 mg/kg as 50 mg/ml solution in 50%Labrasol 50%H20 (Cmax - 3.4uM, Tmax - 1hr as 25 mg/ml in 0.5% CMC; Cmax - 0.4uM, Tmax - 2hr as 100 mg/ml in PEG400)

[16] 20 mg/kg as 10 mg/ml solution in 10% DMSO 10% cremophor 80% saline (could not dissolve it in PEG, Labrasol or PG at 50 mg/ml)

[17] 50 mg/kg as 25 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.07uM, Tmax - 3hr as 25 mg/ml in 0.5% CMC)

[18] 50 mg/kg as 100 mg/ml in PEG400 or as 25 mg/ml in 0.5% CMC (Cmax - 0.2uM, Tmax - 0.25 hr as 50 mg/ml solution in 50%Labrasol 50%H2O)

[19] 50 mg/kg as 50 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.9uM Tmax - 1hr as 100 mg/ml in PEG400; Cmax - 0.9uM Tmax - 0.5hr as 100 mg/ml in PG; Cmax - 0.4uM Tmax - 1hr as 25 mg/ml in 0.5%CMC)

[20] 50 mg/kg as 50 mg/ml solution in 50%Labrasol 50%H2O (Cmax - 0.5uM; Tmax - 3hr as 25 mg/ml in 0.5%CMC)

[21] 50 mg/kg as 50 mg/ml solution in Labrasol/H2O 1/1 (Cmax - 1.2uM, Tmax - 7hr as 100 mg/ml in PEG400; Cmax - 0.7uM, Tmax - 3hr as 25 mg/ml in 0.5% CMC; Cmax - 1uM, Tmax - 7hr as 100mg/ml in PG)

[22] 50 mg/kg as 25 mg/ml suspention in 0.5%CMC (Cmax - 3.3uM, Tmax - 5hr as 50 mg/ml in Labrasol/H20 1/1)

[23] 50 mg/kg as 25mg/ml solution in Labrasol/H2O 1/1 (Cmax-2.5uM, Tmax-7hr as 100 mg/ml in PG; Cmax-3.6uM, Tmax-7hr as 25 mg/ml in 0.5%CMC)

[24] 50 mg/kg as 50 mg/ml in 50%Labrasol 50%H2O (Cmax -1.9uM, Tmax - 5hr as 25 mg/ml in 1%CMC)

In Vivo Tests

Materials and Methods:

Adult male Sprague-Dawley rats were purchased from Harlan Sprague Dawley (San Diego). Animals were housed two per cage and maintained in a temperature- controlled room (22 ± 2°C) with a photoperiod of 12 hours light/12 hours dark (lights on at 0600 hours). Rat chow (Teklad LM-485 rat diet, Madison, WI) and tap water were provided *ad libitum*.

Animal models to assess activity of GnRH antagonists:

Model #1: Castrated Male Rat Model

Surgical removal of the gonads removes circulating testosterone and eliminates the negative feedback of testosterone on the hypothalamus. As a result, GnRH is elevated and consequently elevates LH. A GnRH antagonist would be expected to reduce GnRH mediated elevations of LH levels. Antide, a GnRH peptide antagonist, reduces LH levels in castrated rats. The model seems suitable for evaluating small molecule GnRH antagonists.

Male Sprague-Dawley (200-225 g) rats were castrated via the scrotal approach under halothane anesthesia. Animals were allowed 14 days post operative recovery prior to study. Thirteen days following castration, animals were anesthetized with halothane and instrumented with indwelling jugular vein cannula. Details of the cannulation procedure have been described previously (Harms et al., *Applied Physiol.* 36:391-398 (1974)).

On study day, animals were allowed to acclimate to the procedure room while residing in their home cage. Basal blood samples were drawn from all animals. Immediately following basal sampling, vehicle or test compounds were administered by intravenous (iv), intraperitoneal (ip), intramuscular (im) or oral (po) routes. Test compounds were formulated in vehicles specified in Table 3. Blood samples were drawn into heparin containing tubes at multiple time points post treatment. Blood was centrifuged immediately, plasma collected and stored in -20° freezer until assayed. Plasma samples were analyzed using DSL-4600 ACTIVE LH coated-tube immunoradiometric assay kit from Diagnostic Systems Laboratories, Inc. Webster, Texas. Cremophor EL obtained from Sigma, St. Louis, MO.

The results of the GnRH antagonist experiments with various concentrations (1.0-100 mg/kg) in different administration routes (iv, im, and po) of GnRH agents, Compounds C23, and B52 in the above castrated rat model are shown in Figures 1- 4.

Model #2: Intact Male Rat

Testosterone is a hormone regulated by the hypothalamic-pituitary-gonadal axis. GnRH is secreted in pulses from the hypothalamus and stimulates the anterior pituitary gland to release gonadotropic hormones LH and FSH. Testosterone is produced when the testes are stimulated by LH. A GnRH antagonist is expected to reduce testosterone levels by inhibiting GnRH stimulation of LH release.

Male Sprague-Dawley (250-275 g) rats were single-housed and allowed to acclimate for 1 week prior to study. On study day animals were treated with vehicles specified in Table 3) or test compound. Blood samples were obtained via indwelling jugular vein cannulae implanted 5 days prior to study (Harms et al., *Applied Physiol.* 36:391-398 (1974)). Blood samples were drawn into heparin containing tubes at multiple time points post treatment. Blood was centrifuged immediately, plasma collected and stored in -20° freezer until assayed. Plasma samples were analyzed using DSL-4000 ACTIVE Testosterone coated-tube radioimmunoassay kit from Diagnostic Systems Laboratories, Inc. Webster, TX.

The results of the GnRH antagonist experiments with various concentrations (1.0 – 100 mg/kg) in administration routes (iv, im, and po) of GnRH agents, Compounds C23, B3, C2, B52, and B89 in the above intact rat model are shown in Figures 5-10.

Pharmaceutical Compositions

The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of the Formula I, II, or III is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Oral Composition

To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I, II or III is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

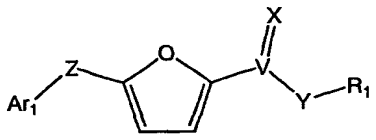
Intraocular Composition

To prepare a sustained release pharmaceutical composition for intraocular delivery, a compound of Formula I, II or III is suspended in a neutral, isotonic solution of hyaluronic acid (1.5% conc.) in a phosphate buffer (pH 7.4) to form a 1% suspension, which is suitable for intraocular administration.

It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Thus, scope of the invention should be understood to be defined not by the foregoing description, but by the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



(I)

wherein:

Ar_1 is a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$,

$-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

Z is O, S, SO, SO_2, or $N(R_f)$ where R_f is hydrogen or an alkyl or -O-alkyl group;

V is SO, S, or C;

X is O, N or S,

Y is O or $N(R_f)$ where R_f is hydrogen or an alkyl or -O-alkyl group; and

R_1 is an unsubstituted aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group, or an alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -N-alkyl, or -O-alkyl group substituted with one or more substituent groups independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said substituent group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$,

$-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, $-C(O)NHC(O)H$, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -N-alkyl, or -O-alkyl; where at least one of the substituent groups on said alkyl, alkenyl, or alkynyl group is said unsubstituted or substituted aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group.

2. A compound, salt, prodrug, or metabolite according to claim 1, wherein: Z is O.

3. A compound, salt, prodrug, or metabolite according to claim 1, wherein: V is C; and X is O.

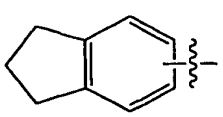
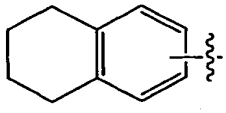
4. A compound, salt, prodrug, or metabolite according to claim 1, wherein: Y is NH.

5. A compound or salt according to claim 1, wherein: R_1 is an aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group unsubstituted or substituted with one or more substituent groups independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH,

-C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_z$CN where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, -NO_2, -CN, -$(CH_2)_z$-CN where z is an integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

6. A compound or salt according to claim 5, wherein: Z is O; V is C; Y is NH; and X is O.

7. A compound or salt according to claim 6, wherein Ar_1 is a

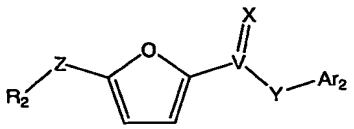
 or 

group unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogens, alkyl, =O, -O-alkyl, -C(O)-alkyl, -N(alkyl)(alkyl), -NH(alkyl), -OH, $-NH_2$, -C(O)-N(alkyl)(alkyl), -C(O)-N(H)(alkyl), and -C(O)-H.

8. A compound or salt according to claim 7, wherein: R_1 is a heteroaryl group unsubstituted or substituted with one or more substituent groups independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is

hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

9. A compound represented by Formula (II):



(II)

wherein:

Ar_2 is a six-membered heteroaryl group unsubstituted or substituted with one or more substituents selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$,

$-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

Z is O, S, SO, SO_2, or $N(R_f)$ where R_f is hydrogen or an alkyl or –O-alkyl group;

V is S or C;

X is S, O, or N;

Y is O or $N(R_f)$ where R_f is hydrogen or an alkyl or -O-alkyl group; and

R_2 is an alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$,

-OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, -NO_2, -CN, -$(CH_2)_z$-CN where z is an integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

10. A compound, salt, prodrug, or metabolite according to claim 9, wherein: Z is O.

11. A compound, salt, prodrug, or metabolite according to claim 9, wherein: V is C; and X is O.

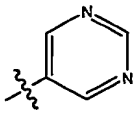
12. A compound, salt, prodrug, or metabolite according to claim 9, wherein: Y is NH.

13. A compound, salt, prodrug, or metabolite according to claim 9, wherein: R_2 is an aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_z$CN where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2,

$-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

14. A compound, salt, prodrug, or metabolite according to claim 13, wherein: Z is O; V is C; Y is NH; and X is O.

15. A compound or salt according to claim 9, wherein: Ar_2 is



unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH,

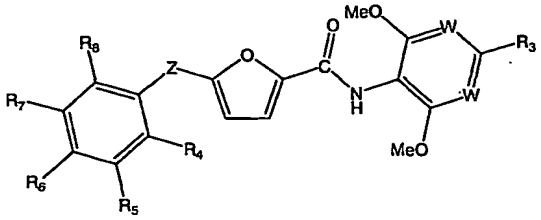
-OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH_2)$_z$CN where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, -NO_2, -CN, -(CH_2)$_z$-CN where z is an integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

16. A compound or salt according to claim 15, wherein: Z is O; V is C; X is O; and Y is NH.

17. A compound or salt according to claim 16, wherein: R_2 is a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group

unsubstituted or substituted with one or more substituents selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH_2, -NHC(NH)NH_2, -C(S)NH_2, -NHC(S)NH_2, -NHC(O)NH_2, -S(O_2)H, -S(O)H, -NH_2, -C(O)NH_2, -OC(O)NH_2, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O_2)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO_2C(O)OH, -NHSH, -NHS(O)H, -$NHSO_2$H, -C(O)SH, -C(O)S(O)H, -C(O)S(O_2)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO_2)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO_2)H, -S(O_2)NH_2, -S(O)NH_2, -SNH_2, -NHCS(O_2)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, -NO_2, -CN, -$(CH_2)_z$-CN where z is an integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

18. A compound represented by Formula (III):



(III)

wherein:

R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of: hydrogen; halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more

substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

or any two of R_4, R_5, R_6, R_7 and R_8 together with the phenyl ring to which they are attached form a fused polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted

alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

Z is S, SO, SO_2, O, or $N(R_f)$ where R_f is hydrogen or an alkyl or -O-alkyl group;

each W is independently N or C; and

R_3 is hydrogen; halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from

0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -$C(O)NR_c$, -$C(O)OR_c$, -$C(O)R_c$, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -$OC(O)OR_c$, -$OC(O)NR_cR_c$, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

19. A compound, salt, prodrug, or metabolite according to claim 18, wherein: Z is O.

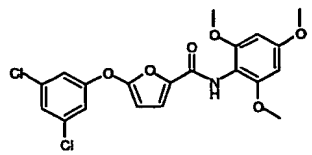
20. A compound, salt, prodrug, or metabolite according to claim 18, wherein: each W is N.

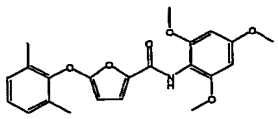
21. A compound or salt according to claim 18, wherein: Z is O; and each W is N.

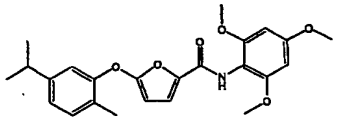
22. A compound or salt according to claim 21, wherein: R_6 and R_7 together with the phenyl to which they are attached form a fused polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, =O, -O-alkyl, -CO-alkyl, -N(alkyl)(alkyl), -NH(alkyl), -OH, $-NH_2$, and -CO-H groups.

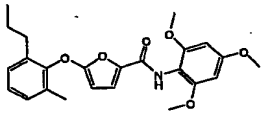
23. A compound or salt according to claim 22, wherein: R_3 is -NH–alkyl-$N(R_d)(R_e)$ or -N(alkyl)–alkyl-$N(R_d)(R_e)$ where R_d and R_e are each independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, -COR_c, -$COOR_c$, -O-CO-O-R_c, -O-CO-R_c, -OH, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, or R_d and R_e together cyclize to form part of a heteroaryl or heterocycloalkyl group, where R_c is as previously defined.

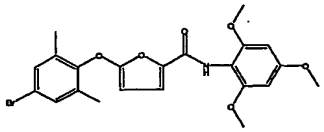
24. A compound selected from the group consisting of:

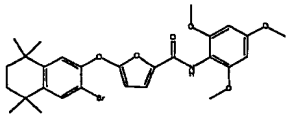


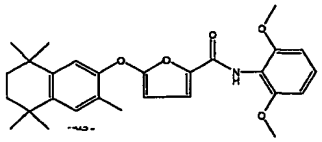


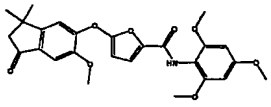


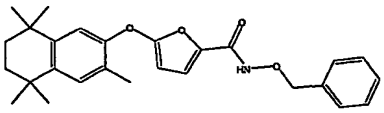


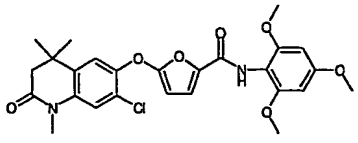


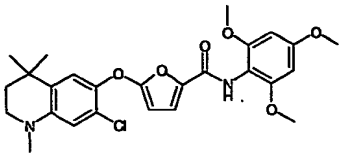


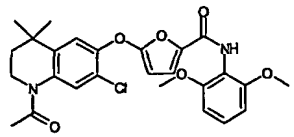


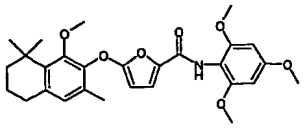


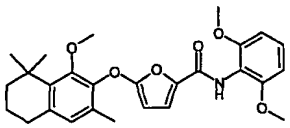


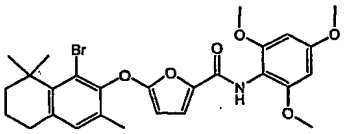


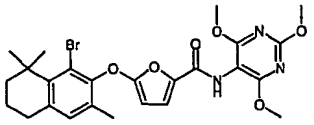


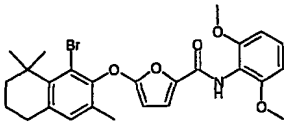


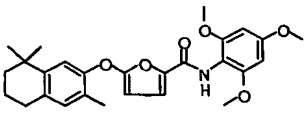


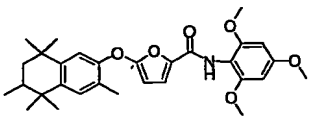


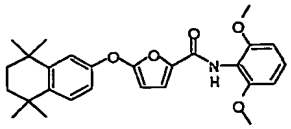


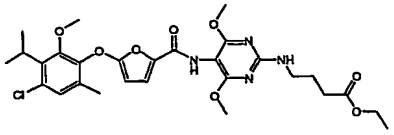


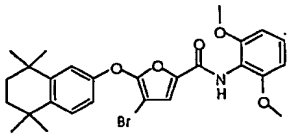


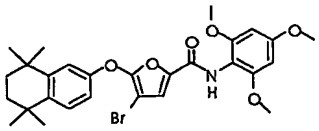


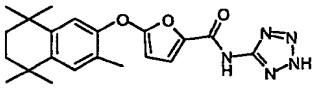


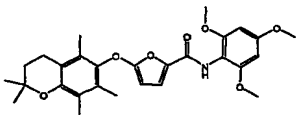


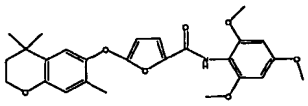


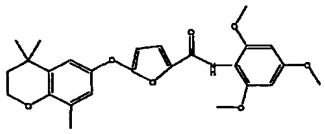


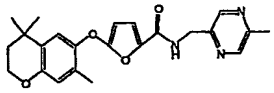


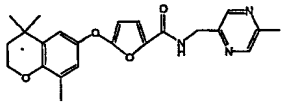


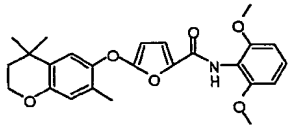


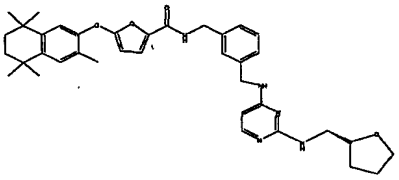


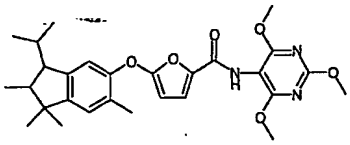


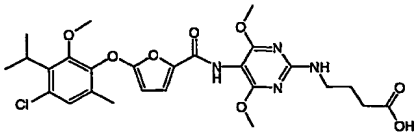


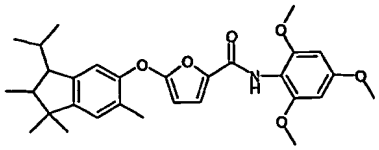


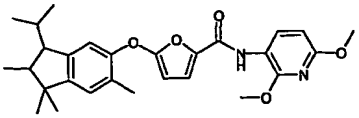


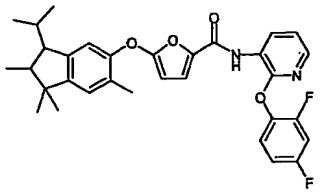


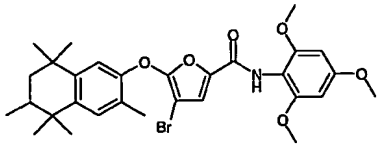


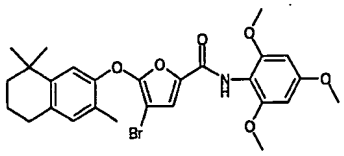


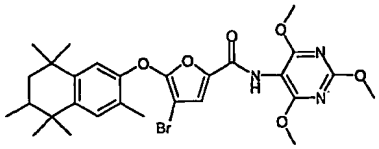


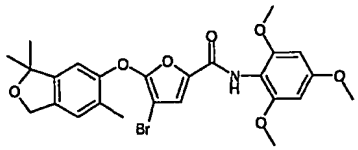


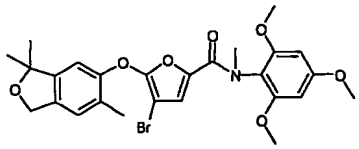


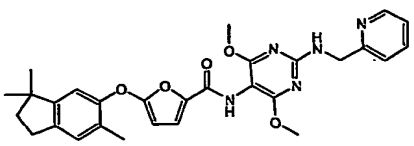


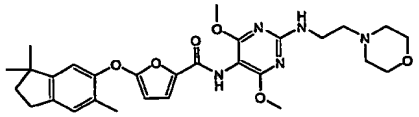


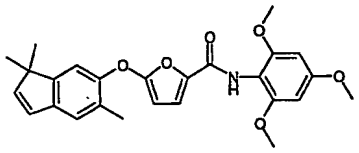


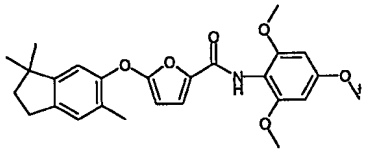


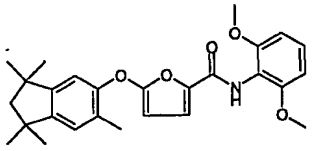


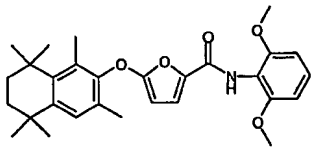


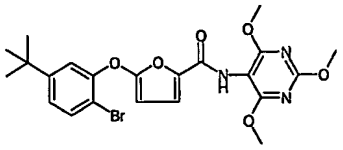


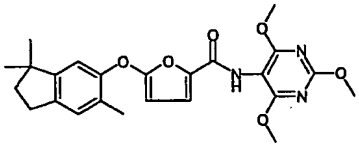


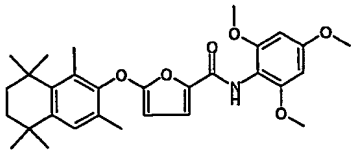


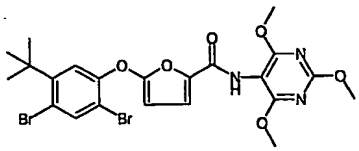


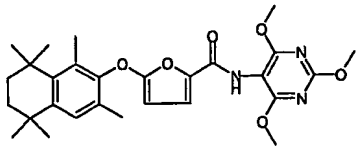


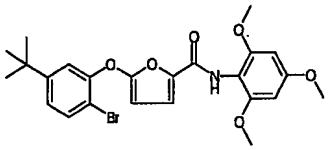


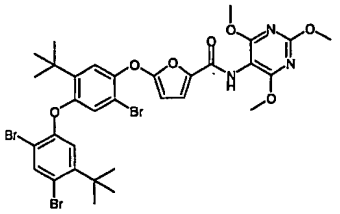


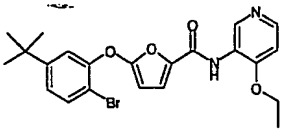


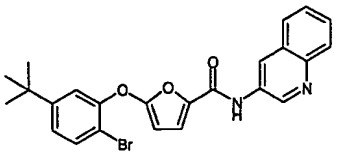


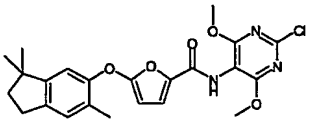


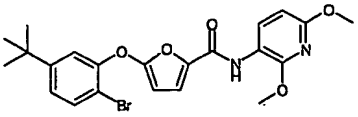


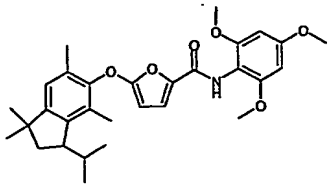


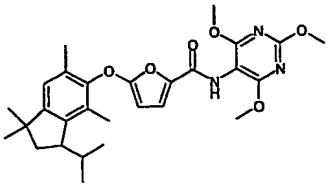


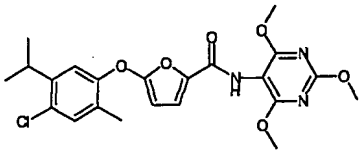


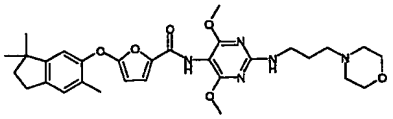


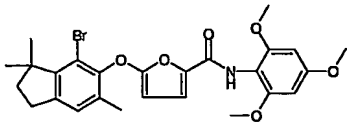


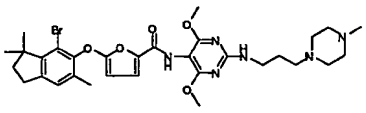


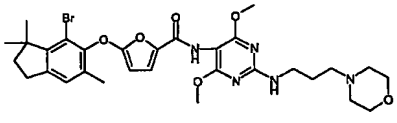


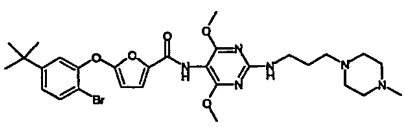


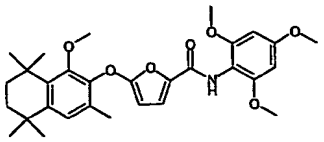


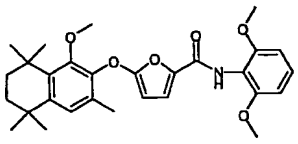


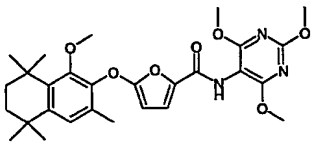


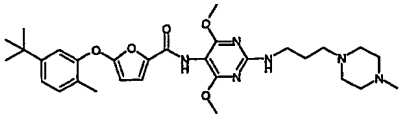


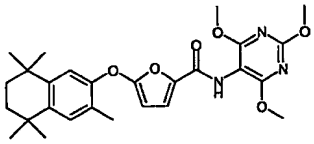


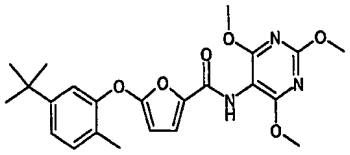


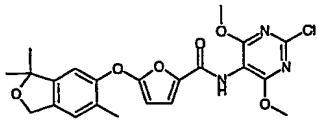


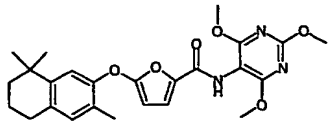


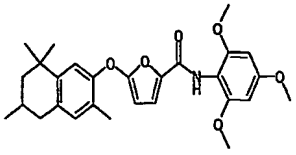


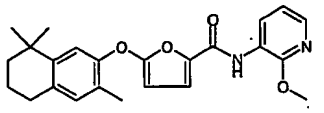


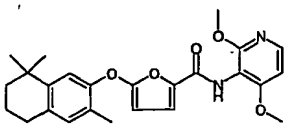


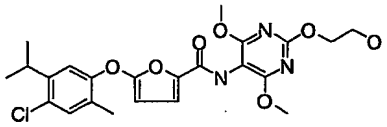


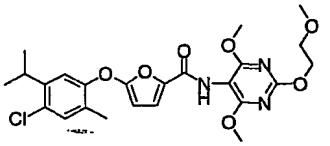


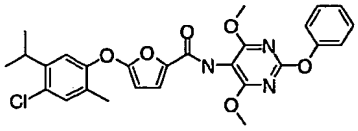


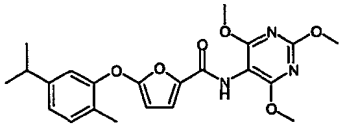


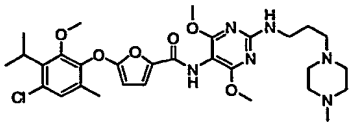


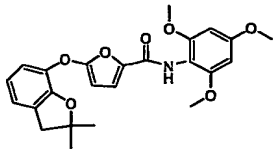












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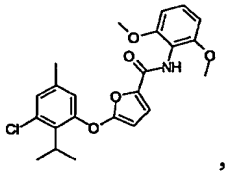

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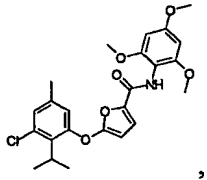

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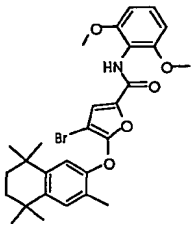

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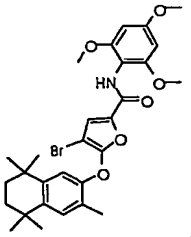

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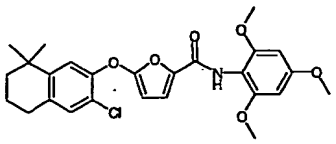

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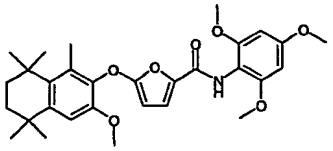

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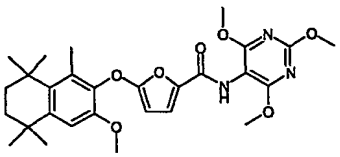

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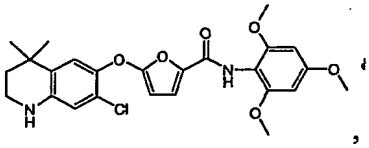

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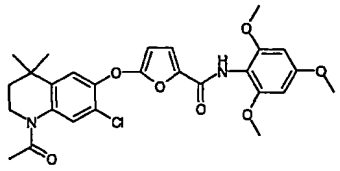

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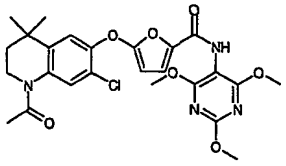

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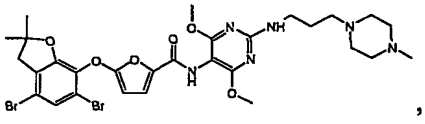

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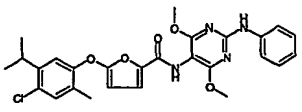

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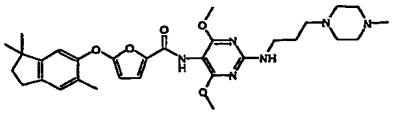

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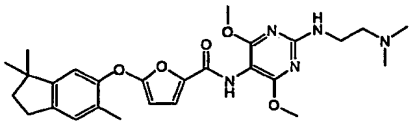

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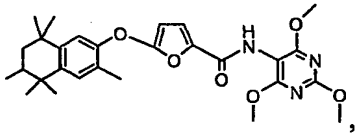

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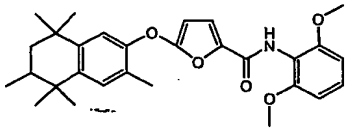

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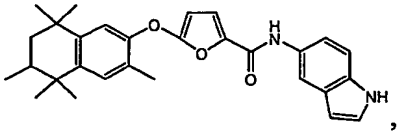

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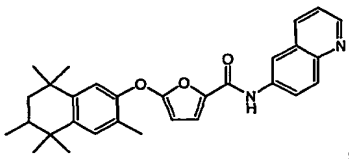

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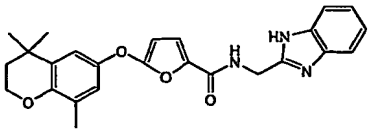
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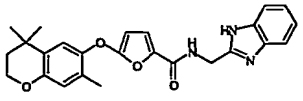
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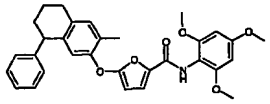
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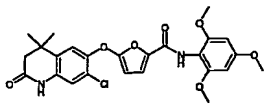
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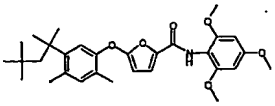
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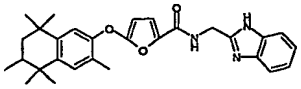
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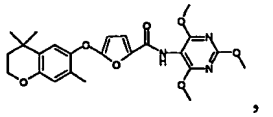
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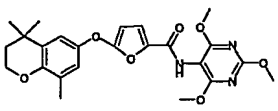

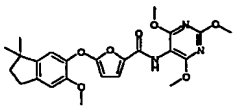
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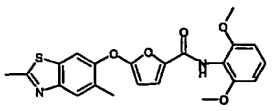
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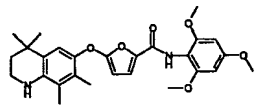
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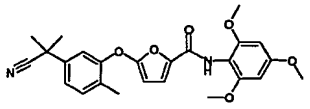
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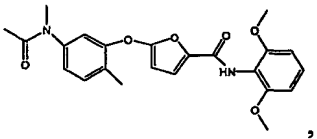
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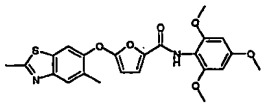
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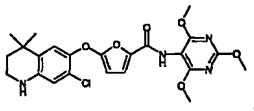
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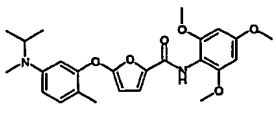
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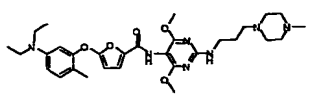

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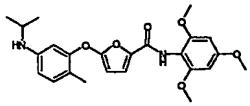

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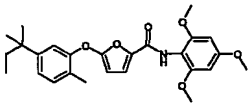

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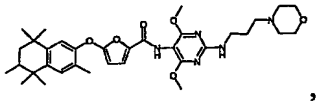

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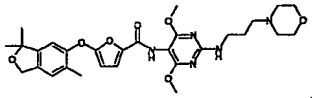

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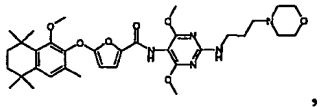

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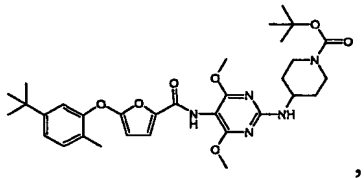

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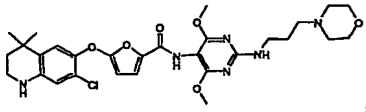

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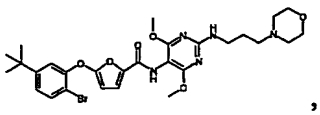
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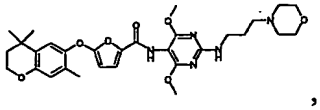
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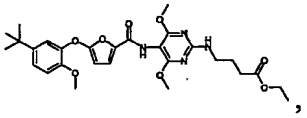
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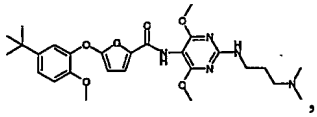
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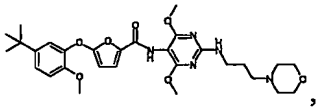
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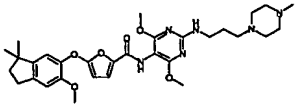
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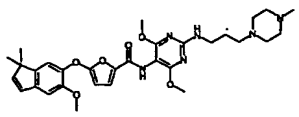

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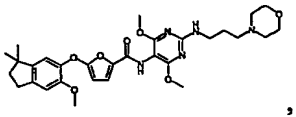

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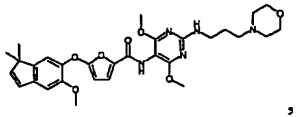

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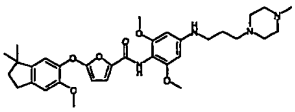

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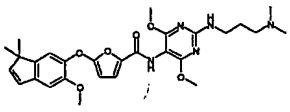

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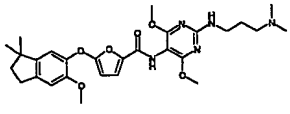

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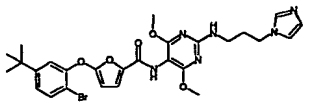

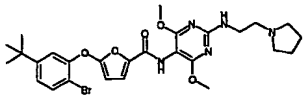

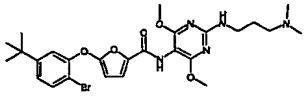

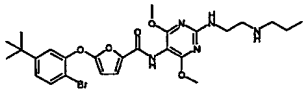

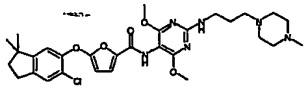

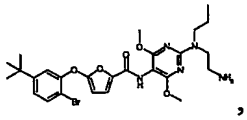

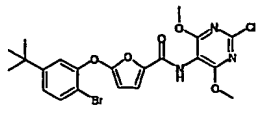

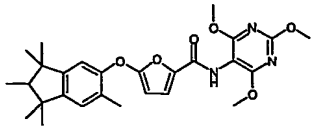

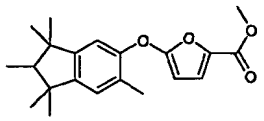

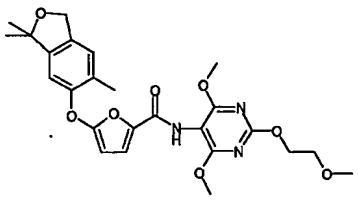

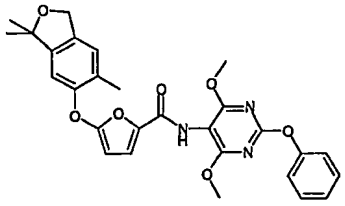

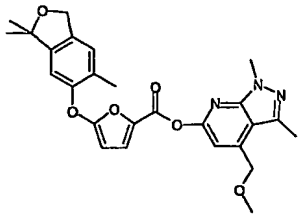

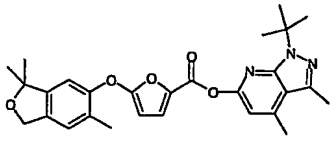

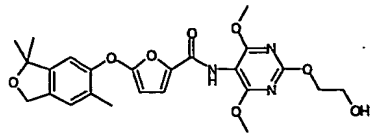
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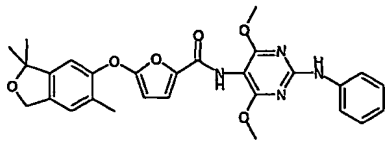
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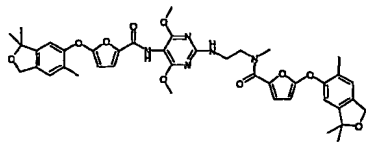
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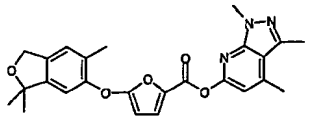
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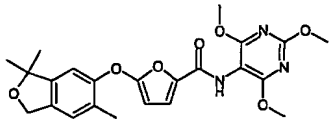
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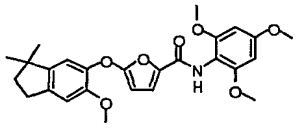
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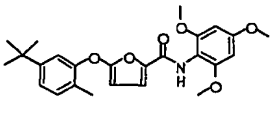
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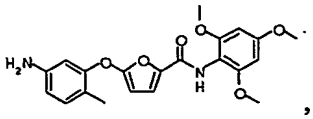
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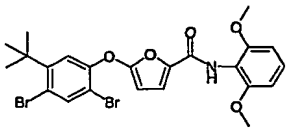
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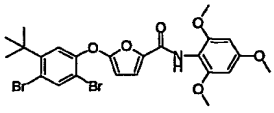
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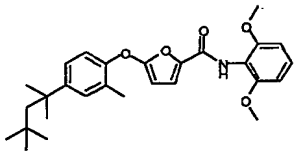
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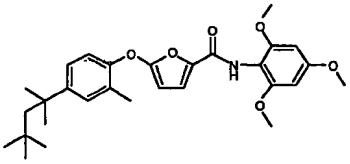
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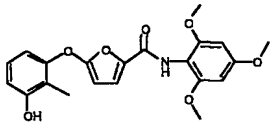
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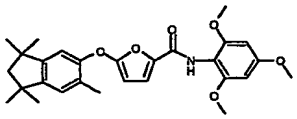
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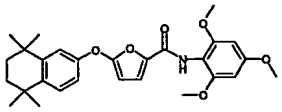
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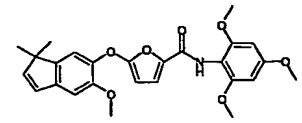
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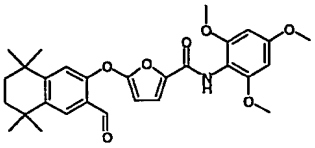
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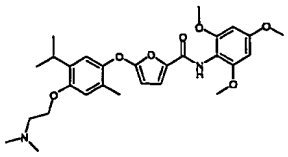
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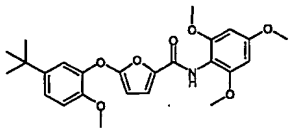
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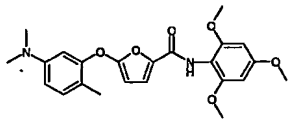
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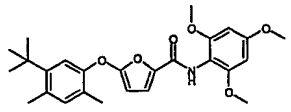
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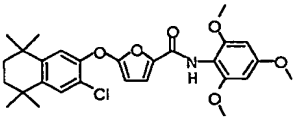
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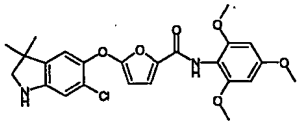
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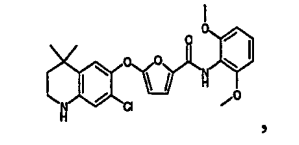
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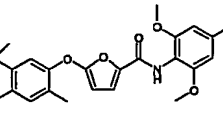
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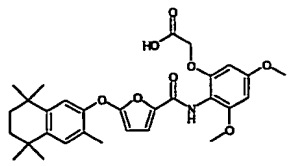
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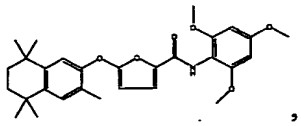
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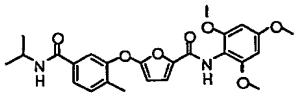
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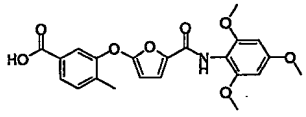
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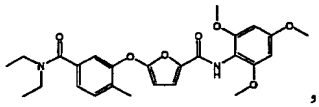
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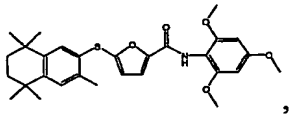
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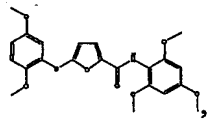
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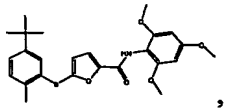
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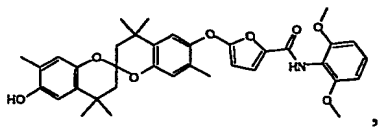

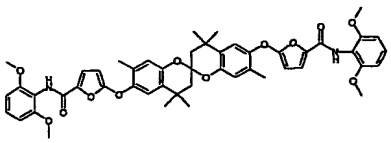

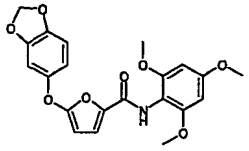

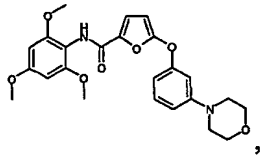

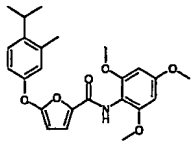

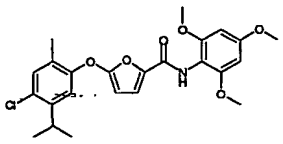

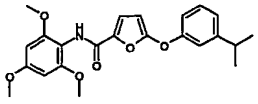

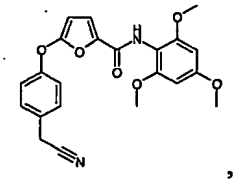

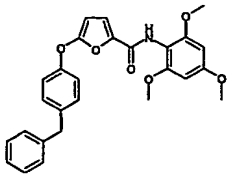

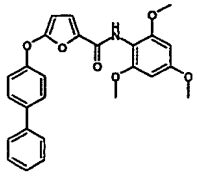

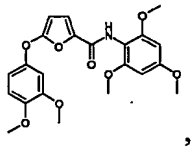

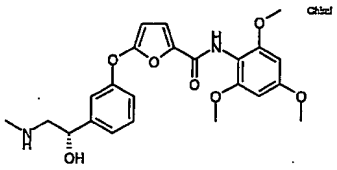

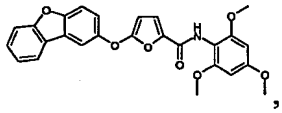

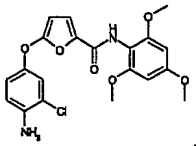

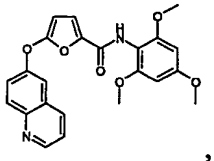

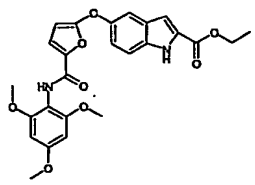

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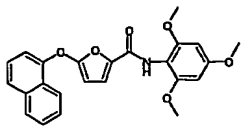

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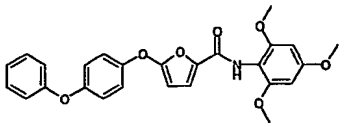

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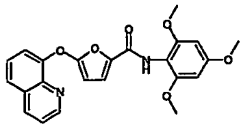

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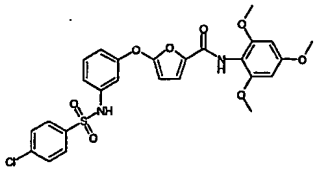

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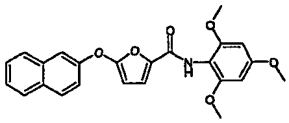

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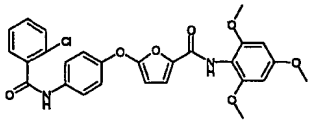

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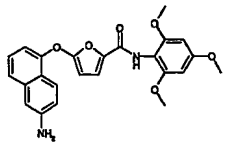

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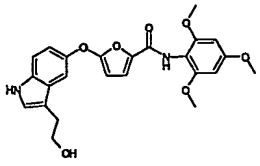

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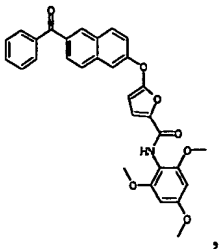

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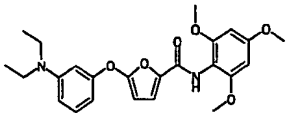

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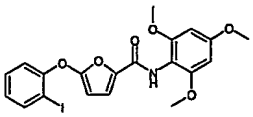

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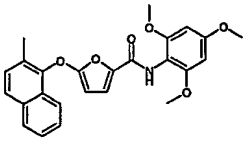

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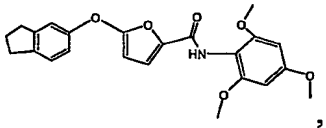

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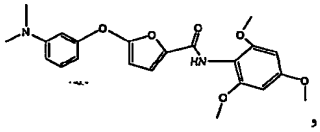

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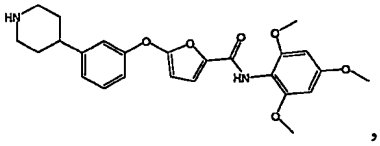

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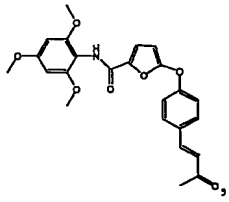
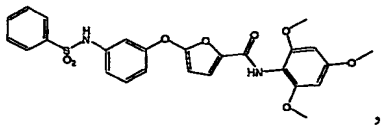
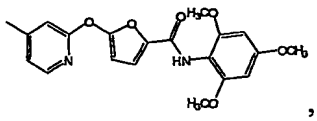
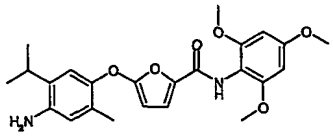
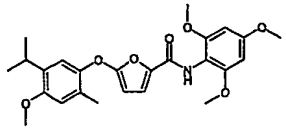
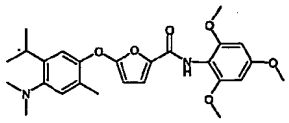


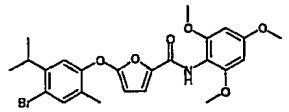


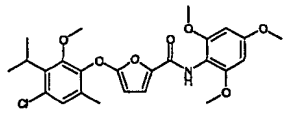












or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising: a therapeutically effective amount of an agent selected from the group consisting of compounds and salts as defined in claim 25; and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition comprising: a therapeutically effective amount of an agent selected from the group consisting of compounds, salts, prodrugs, and metabolites as defined in claim 1; and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising: a therapeutically effective amount of an agent selected from the group consisting of compounds, salts, prodrugs, and metabolites as defined in claim 9; and a pharmaceutically acceptable carrier.

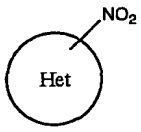
28. A pharmaceutical composition comprising: a therapeutically effective amount of an agent selected from the group consisting of compounds, salts, prodrugs, and metabolite as defined in claim 18; and a pharmaceutically acceptable carrier.

29. A method for regulating the secretion of gonadotropins in a mammal, comprising administering a therapeutically effective amount of a compound, salt, prodrug, or metabolite as defined in claim 1.

30. A method for regulating the secretion of gonadotropins in a mammal, comprising administering a therapeutically effective amount of a compound, salt, prodrug, or metabolite as defined in claim9.

31. A method for regulating the secretion of gonadotropins in a mammal, comprising administering a therapeutically effective amount of a compound, salt, prodrug, or metabolite as defined in claim 18.

32. A process of making a compound of Formula IVa:



(IVa)

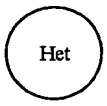
wherein: Het is a 5- or 6-membered heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of: halogens; -CN; and $-NO_2$; and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is an integer from 0 to 4, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups, each said group being unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is an integer from 0 to 4, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl,

unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents may cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where R_c is hydrogen, unsubstituted alkyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

comprising the steps of:

(a) preparing a nitrating reagent by adding trifluoromethanesulfonic anhydride to 2-tetramethylammonium nitrate in a polar solvent; and

(b) conducting a reaction of said nitrating reagent with a compound of Formula IV:



(IV)

wherein Het is as previously defined;

to form said compound of the formula IVa.

33. A process according to claim 32, wherein Het is a heteroaryl selected from the group consisting of furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, pyrrole, oxazole, thiazole, imidazole, pyrazole, and 1,3,5-triazine.

34. A process according to claim 32, wherein said solvent is dichloromethane, chloroform, dichloroethane, or nitromethane.

35. A process according to claim 32, wherein said forming step (a) further comprises adding the 2-tetramethylammonium nitrate to the polar solvent prior to the adding of said trifluoromethanesulfonic anhydride.

36. A process according to claim 32, further comprising cooling said nitrating reagent to a temperature of from 0°C to -80°C and then adding said compound of Formula IV to the cooled nitrating reagent.

37. A process according to claim 32, further comprising:

(c) quenching the reaction and then separating out and purifying the compound of Formula IV.

38. A process according to claim 32, wherein steps (a) and (b) are performed under an inert atmosphere.